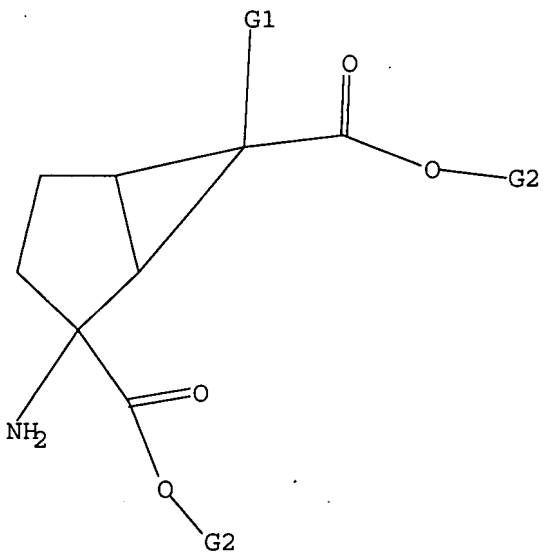
10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

=>
Uploading C:\Program Files\Stnexp\Queries\2007 cases\10562010\core no Y.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 H,X
G2 H,Cb,Cy,Ak

Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 10:45:08 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 108 TO ITERATE

100.0% PROCESSED 108 ITERATIONS 39 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1537 TO 2783
PROJECTED ANSWERS: 406 TO 1154

L2 39 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 10:45:19 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 2198 TO ITERATE

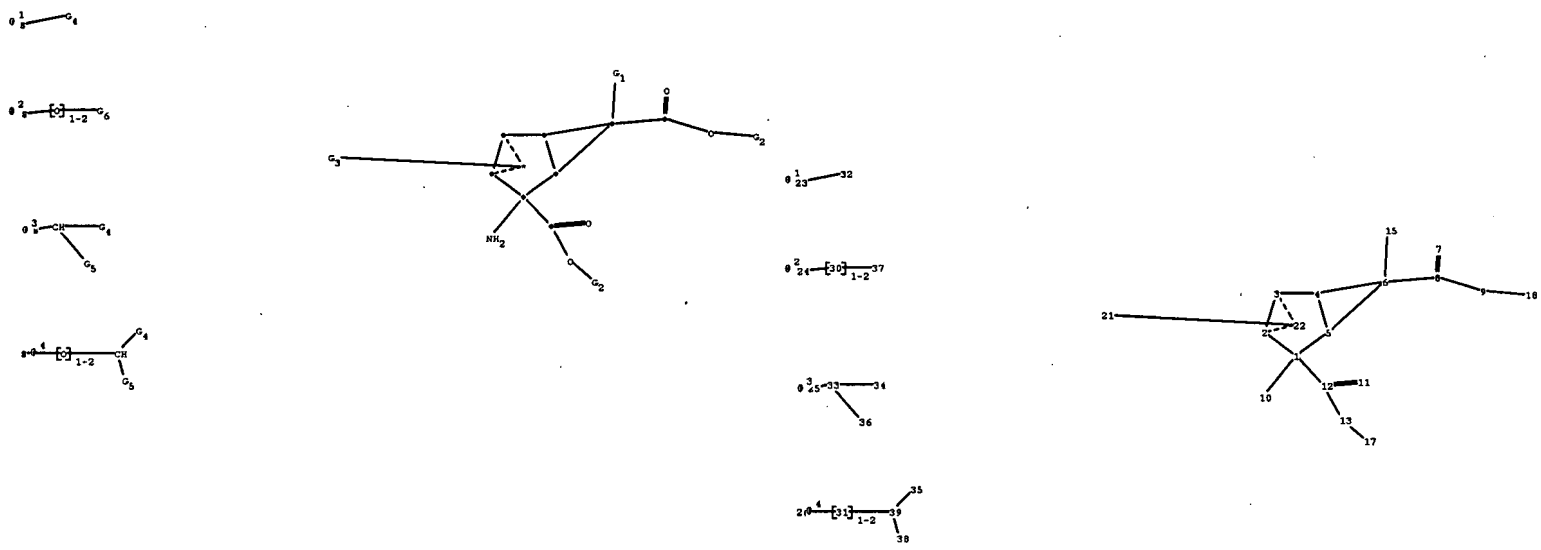
100.0% PROCESSED 2198 ITERATIONS 730 ANSWERS
SEARCH TIME: 00.00.01

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

L3 730 SEA SSS FUL L1

=>

C:\Program Files\Stnexp\Queries\2007 cases\10562010\core with Y.str



chain nodes :
7 8 9 10 11 12 13 15 17 18 21 23 24 25 26 30 31 32 33 34 35 36 37 38 39
ring nodes :
1 2 3 4 5 6
chain bonds :
1-10 1-12 6-8 6-15 7-8 8-9 9-18 11-12 12-13 13-17 23-32 24-30 25-33 26-31 30-37 31-39
33-34 33-36 35-39 38-39
ring bonds :
1-2 1-5 2-3 3-4 4-5 4-6 5-6
exact/norm bonds :
1-2 1-5 1-10 2-3 3-4 4-5 4-6 5-6 6-15 7-8 8-9 9-18 11-12 12-13 13-17 23-32 24-30
25-33 26-31 30-37 31-39 33-34 33-36 35-39 38-39
exact bonds :
1-12 6-8

G1:H,X

G2:H,Cb,Cy,Ak

G3:NH2,H,[*1],[*2],[*3],[*4]

G4:H,Cb,Cy,Hy,Ak

G5:H,Cb,Cy,Hy,Ak

G6:Cb,Cy,Hy,Ak

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 15:CLASS 17:CLASS 18:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

```
=>
Uploading C:\Program Files\Stnexp\Queries\2007 cases\10562010\core with Y.str

L4      STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l4
SAMPLE SEARCH INITIATED 10:46:20 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      108 TO ITERATE

100.0% PROCESSED      108 ITERATIONS                                39 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1537 TO     2783
PROJECTED ANSWERS:             406 TO     1154

L5          39 SEA SSS SAM L4

=> s l4 sss full
FULL SEARCH INITIATED 10:46:27 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     2198 TO ITERATE

100.0% PROCESSED     2198 ITERATIONS                           730 ANSWERS
SEARCH TIME: 00.00.01

L6          730 SEA SSS FUL L4

=> s l6 subset=l3
ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):sample
SAMPLE SUBSET SEARCH INITIATED 10:46:55 FILE 'REGISTRY'
SAMPLE SUBSET SCREEN SEARCH COMPLETED -       39 TO ITERATE

100.0% PROCESSED       39 ITERATIONS                                39 ANSWERS
SEARCH TIME: 00.00.01

PROJECTIONS (WITHIN SPECIFIED SUBSET):           ONLINE  **COMPLETE**
PROJECTED ITERATIONS (WITHIN SPECIFIED SUBSET):          406 TO     1154
PROJECTED ANSWERS (WITHIN SPECIFIED SUBSET):             406 TO     1154

L7          39 SEA SUB=L3 SSS SAM L4

=> s l6 subset=l3
ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):full
FULL SUBSET SEARCH INITIATED 10:47:03 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -      730 TO ITERATE

100.0% PROCESSED      730 ITERATIONS                           730 ANSWERS
SEARCH TIME: 00.00.02
```

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

=> d his

(FILE 'HOME' ENTERED AT 10:44:10 ON 26 JUL 2007)

FILE 'REGISTRY' ENTERED AT 10:44:45 ON 26 JUL 2007

```
L1             STRUCTURE UPLOADED
L2              39 S L1
L3             730 S L1 SSS FULL
L4             STRUCTURE UPLOADED
L5              39 S L4
L6             730 S L4 SSS FULL
L7              39 S L6  SUB=L3 SAMPLE
L8             730 S L6  SUB=L3 FULL
```

FILE 'HCAPLUS' ENTERED AT 10:47:35 ON 26 JUL 2007

```
L9              21 S L7
L10            190 S L6 OR L8
L11           4615 S "METABOTROPIC GLUTAMATE RECEPTOR"
L12            145 S L10 AND L11
```

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

USPGPub via STN
hm
7/30/07

```
=> e US20060142388/apps
E1            1     US2006-DS263185/PRN
E2            1     US2006-DS263364/PRN
E3            0 --> US20060142388/AP
E4            0     US20060142388/PRN
E5            1     US2007-474898/AP
E6            1     US2007-495394/AP
E7            1     US2007-520878/AP
E8            1     US2007-524672/AP
E9            1     US2007-525241/AP
E10           1     US2007-528724/AP
E11           1     US2007-529680/AP
E12           1     US2007-530406/AP

=> e US20060142388/ap,prn,pn
E1            1     US2006014237/PN
E2            1     US2006014238/PN
E3            0 --> US20060142388/AP
E4            0     US20060142388/PRN
E5            0     US20060142388/PN
E6            1     US2006014239/PN
E7            1     US2006014240/PN
E8            1     US2006014241/PN
E9            1     US2006014242/PN
E10           1     US2006014243/PN
E11           1     US2006014244/PN
E12           1     US2006014245/PN

=> s US20060142388/apps
              0 US20060142388/AP
              0 US20060142388/PRN
L1            0 US20060142388/APPS
                  (US20060142388/AP,PRN)

=> s US2006-142388/apps
              0 US2006-142388/AP
              0 US2006-142388/PRN
L2            0 US2006-142388/APPS
                  (US2006-142388/AP,PRN)

=> e US2006-142388/apps
E1            1     US2006-10     595089/AP
E2            1     US2006-134249/AP
E3            0 --> US2006-142388/AP
E4            0     US2006-142388/PRN
E5            1     US2006-150233P/PRN
E6            1     US2006-164163/AP
E7            1     US2006-164163/PRN
E8            1     US2006-182354/AP
E9            1     US2006-187833P/PRN
E10           1     US2006-194875/AP
E11           1     US2006-203859/AP
E12           1     US2006-208563/PRN
```

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

7/26/07

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTAMLL1621

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS 3	MAR 16	CASREACT coverage extended
NEWS 4	MAR 20	MARPAT now updated daily
NEWS 5	MAR 22	LWPI reloaded
NEWS 6	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS 7	APR 02	JICST-EPLUS removed from database clusters and STN
NEWS 8	APR 30	GENBANK reloaded and enhanced with Genome Project ID field
NEWS 9	APR 30	CHEMCATS enhanced with 1.2 million new records
NEWS 10	APR 30	CA/CAplus enhanced with 1870-1889 U.S. patent records
NEWS 11	APR 30	INPADOC replaced by INPADOCDB on STN
NEWS 12	MAY 01	New CAS web site launched
NEWS 13	MAY 08	CA/CAplus Indian patent publication number format defined
NEWS 14	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS 15	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS 16	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS 17	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS 18	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS 19	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS 20	JUN 29	STN Viewer now available
NEWS 21	JUN 29	STN Express, Version 8.2, now available
NEWS 22	JUL 02	LEMBASE coverage updated
NEWS 23	JUL 02	LMEDLINE coverage updated
NEWS 24	JUL 02	SCISEARCH enhanced with complete author names
NEWS 25	JUL 02	CHEMCATS accession numbers revised
NEWS 26	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 27	JUL 16	CAplus enhanced with French and German abstracts
NEWS 28	JUL 18	CA/CAplus patent coverage enhanced
NEWS 29	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:28:26 ON 26 JUL 2007

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 14:28:51 ON 26 JUL 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 25 JUL 2007 HIGHEST RN 943407-83-8
DICTIONARY FILE UPDATES: 25 JUL 2007 HIGHEST RN 943407-83-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\2007 cases\10562010\core with Y.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

```
=> s l1
SAMPLE SEARCH INITIATED 14:29:17 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      108 TO ITERATE

100.0% PROCESSED      108 ITERATIONS                          39 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1537 TO     2783
PROJECTED ANSWERS:             406 TO     1154

L2            39 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 14:29:22 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    2198 TO ITERATE

100.0% PROCESSED     2198 ITERATIONS                         730 ANSWERS
SEARCH TIME: 00.00.01

L3           730 SEA SSS FUL L1

=> fil hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             172.10     172.31

FILE 'HCAPLUS' ENTERED AT 14:29:28 ON 26 JUL 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 26 Jul 2007  VOL 147 ISS 5
FILE LAST UPDATED: 25 Jul 2007  (20070725/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l3
L4           190 L3

=> s l2
L5            21 L2
```
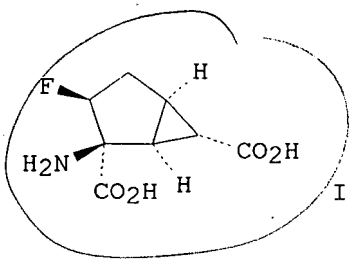

```
=> s "metabotropic glutamate receptor"
          6633 "METABOTROPIC"
        108224 "GLUTAMATE"
          1129 "GLUTAMATES"
        108637 "GLUTAMATE"
                 ("GLUTAMATE" OR "GLUTAMATES")
        709260 "RECEPTOR"
        651411 "RECEPTORS"
        845235 "RECEPTOR"
                 ("RECEPTOR" OR "RECEPTORS")
L6        4615 "METABOTROPIC GLUTAMATE RECEPTOR"
                 ("METABOTROPIC"(W)"GLUTAMATE"(W)"RECEPTOR")

=> s l6 and l3
           190 L3
L7         145 L6 AND L3

=> s l6 and l5
L8          19 L6 AND L5

=> s l6 and l4
L9         145 L6 AND L4

=> d l9 1-145 ibib abs

L9   ANSWER 1 OF 145  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2007:605093  HCAPLUS
DOCUMENT NUMBER:         147:87324
TITLE:                   Stimulation of the metabotropic glutamate 2/3 receptor
                         attenuates social novelty discrimination deficits
                         induced by neonatal phencyclidine treatment
AUTHOR(S):               Harich, Silke; Gross, Gerhard; Bespalov, Anton
CORPORATE SOURCE:        Neuroscience Discovery Research, Abbott, Ludwigshafen,
                         67061, Germany
SOURCE:                  Psychopharmacology (Berlin, Germany) (2007), 192(4),
                         511-519
                         CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER:               Springer GmbH
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Glutamatergic mechanisms are implicated in psychiatric disorders such as
     schizophrenia.  Modulation of glutamatergic neurotransmission via
     stimulation of the metabotropic glutamate 2/3 receptors (mGluR2/3) has
     been shown to reverse a number of behavioral effects of NMDA receptor
     antagonists thus indicating potential antipsychotic activity of mGluR2/3
     agonists.  The present study aimed to evaluate the effects of LY-354740
     (mGluR2/3 agonist) and LY-487379 (mGluR2 potentiator) on social novelty
     discrimination in male Wistar rats that were treated with PCP (10 mg/kg,
     s.c.) on postnatal days 7, 9, and 11.  During each test session (twice a
     week, postnatal days 70-100), an adult exptl. rat was presented with a
     juvenile, untreated rat (4 wk old) for a period of 30 min.  At the end of
     this period, a second (novel) juvenile rat was introduced for 5 min.
     Adult rats spent more time exploring the novel than the familiar juvenile.
     This capacity for social novelty discrimination was impaired in rats that
     received neonatal PCP treatment and the impaired discrimination could be
     reversed by acute treatment with antipsychotic drugs such as clozapine
```

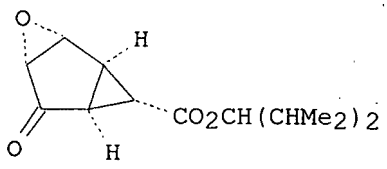
(0.3-3 mg/kg) and the glycine transporter GlyT1 inhibitor SSR-504734 (1-10 mg/kg). Acute pretreatment with LY-354740 (1-10 mg/kg) or LY-487379 (3-30 mg/kg) facilitated social discrimination in rats with PCP administration history without having appreciable effects in controls and without affecting total time spent in social interaction. These results suggest that targeting glutamatergic functions may reverse long-term developmental cognitive deficits produced by PCP.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:331539 HCAPLUS
DOCUMENT NUMBER: 146:500629
TITLE: Scalable synthesis of (+)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid as a potent and selective group II metabotropic glutamate receptor agonist
AUTHOR(S): Sakagami, Kazunari; Kumagai, Toshihito; Taguchi, Takeo; Nakazato, Atsuro
CORPORATE SOURCE: Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Kita-ku, Saitama, 331-9530, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (2007), 55(1), 37-43
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:500629
GI



I



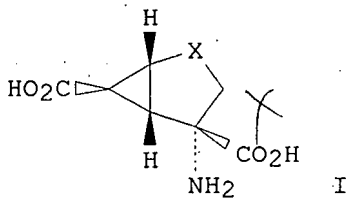
II

AB The potent and selective group II mGluR agonist (+)-I (MGS0008) has been successfully synthesized via a process incorporating the efficient fluorination of epoxide (±)-II as the key step. This method is adaptable to large-scale synthesis to produce (+)-I in multi-gram quantities.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1341533 HCAPLUS
DOCUMENT NUMBER: 146:251680
TITLE: Synthesis and Metabotropic Glutamate Receptor Activity of S-Oxidized Variants of (-)-4-Amino-2-thiabicyclo-[3.1.0]hexane-4,6-dicarboxylate: Identification of Potent, Selective, and Orally Bioavailable Agonists for mGlu2/3 Receptors

AUTHOR(S): Monn, James A.; Massey, Steven M.; Valli, Matthew J.; Henry, Steven S.; Stephenson, Gregory A.; Bures, Mark; Herin, Marc; Catlow, John; Giera, Deborah; Wright, Rebecca A.; Johnson, Bryan G.; Andis, Sherri L.; Kingston, Ann; Schoepp, Darryle D.
CORPORATE SOURCE: Discovery Chemistry and Neuroscience Research Divisions, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (2007), 50(2), 233-240
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:251680
GI



I

AB (-)-4-Amino-2-thiabicyclo-[3.1.0]hexane-4,6-dicarboxylate (-)-I (X = S) (LY389795) is a highly potent and selective agonist of metabotropic glutamate receptors 2 (mGlu2) and 3 (mGlu3). As part of the ongoing research program, S-oxidized variants of this compound, namely both S-stereoisomers of I (X = SO) and I (X = SO2), were synthesized. Each of these chiral heterobicyclic amino acids displaced specific binding of the mGlu2/3 receptor antagonist 3H-2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3-(xanth-9-yl)propanoic acid (3H-LY341495) from membranes expressing recombinant human mGlu2 or mGlu3 and acted as potent agonists in cells expressing these receptor subtypes. Docking of the most potent of these derivs., (SR)-(+)-I [X = SO, (II)] to mGlu2 revealed the possibility of an addnl. H-bond interaction between the sulfoxide oxygen of II with tyrosine residue Y236. Pharmacokinetic anal. of mGlu active enantiomers II and (-)-I (X = SO2) in rats showed each to be well absorbed following oral administration. Consistent with their mGlu2/3 agonist potency and pharmacokinetic properties, both II and (-)-I (X = SO2) blocked phencyclidine-evoked ambulations in a dose-dependent manner, indicating their potential as nonclassical antipsychotic agents.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1340490 HCAPLUS
DOCUMENT NUMBER: 146:177000
TITLE: Effects of metabotropic glutamate 2/3 receptor antagonists in the stress-induced hyperthermia test in singly housed mice
AUTHOR(S): Iijima, Michihiko; Shimazaki, Toshiharu; Ito, Akie; Chaki, Shigeyuki

CORPORATE SOURCE: Psychiatric Diseases and Pain Research, Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Kita-ku Saitama, 331-9530, Japan
SOURCE: Psychopharmacology (Berlin, Germany) (2007), 190(2), 233-239
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The stress-induced hyperthermia (SIH) test in mice has been widely used as models including some physiol. aspects of psychiatric disorders. Mediated by the autonomic nervous system, SIH is commonly known to occur both before and during exposure to stress-inducing or anxiogenic situations. Recently, modulation of the group II metabotropic glutamate (mGlu) 2/3 receptor has been proposed as a novel therapeutic approach for psychiatric disorders. In the present study, the authors evaluated the efficacy of selective mGlu2/3 receptor antagonists and an mGlu2/3 receptor agonist in the SIH test. MGlu2/3 receptor antagonists such as MGS0039 and LY341495 significantly and dose-dependently reduced SIH without affecting basal rectal temps. In contrast, mGlu2/3 receptor agonists such as MGS0008 were ineffective in the SIH test. The attenuation of SIH by MGS0039 was significantly blocked by pretreatment with WAY100635, a serotonin 1A receptor antagonist. In contrast, an AMPA receptor potentiator, CX546 failed to reduce the SIH. Taken together, these results suggest that the blockade of mGlu2/3 receptor may prevent stress-induced autonomic hyperactivity, and that stimulation of the postsynaptic serotonin 1A receptor, but not AMPA receptor, may be involved in this action.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1205530 HCAPLUS
DOCUMENT NUMBER: 146:19224
TITLE: Are compounds acting at metabotropic glutamate receptors the answer to treating depression?
AUTHOR(S): Palucha, Agnieszka
CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences, Krakow, 31343, Pol.
SOURCE: Expert Opinion on Investigational Drugs (2006), 15(12), 1545-1553
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Numerous studies over the last few years have suggested that modulating the glutamatergic system may be an efficient method to achieve an antidepressant effect. Data suggest that metabotropic glutamate receptors (mGlu receptors), related to long-term, modulatory effects on glutamatergic neurotransmission, may be a good target for the development of new, effective and safe therapeutic drugs to treat several CNS disorders including depression and anxiety. Several potent, selective and systemically active orthosteric and allosteric ligands of specific mGlu receptor subtypes have been discovered and these have been tested as potential antidepressants in models of depression in rodents. The mGluR5 antagonists and group II mGlu receptor

antagonists seem to be the most promising compds. with potential antidepressant-like activity; however, the efficacy of mGlu receptor ligands in the clin. setting is still an unanswered question.
REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1103670 HCAPLUS
DOCUMENT NUMBER: 146:335497
TITLE: Differential changes of group II and group III mGluR function in central amygdala neurons in a model of arthritic pain
AUTHOR(S): Li, Weidong; Neugebauer, Volker
CORPORATE SOURCE: Department of Neuroscience and Cell Biology, The University of Texas Medical Branch, Galveston, TX, USA
SOURCE: Journal of Neurophysiology (2006), 96(4), 1803-1815
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Metabotropic glutamate receptors (mGluRs) play important roles in neuroplasticity and disorders such as persistent pain. Group I mGluRs contribute to pain-related sensitization and synaptic plasticity of neurons in the laterocapsular division of the central nucleus of the amygdala (CeLC), although the roles of groups II and III mGluRs are not known. Extracellular single-unit recordings were made from 60 CeLC neurons in anesthetized adult rats. Background activity and evoked responses were measured before and during the development of the kaolin/carrageenan-induced knee-joint arthritis. Drugs were administered into the CeLC by microdialysis before and/or after arthritis induction. A selective group III mGluR agonist (LAP4) inhibited CeLC neurons' responses to stimulation of the knee and ankle in arthritis (n = 7) more potently than under normal conditions (n = 14). A selective group II agonist (LY354740) inhibited responses under normal conditions (n = 12) and became more potent in inhibiting responses to noxious stimulation of the knee in arthritis (n = 10). The effect of LY354740 on innocuous stimulation of the knee and stimulation of the ankle did not change in arthritis. Antagonists for groups II (EGLU, n = 9) and III (UBP1112, n = 8) had no effects under normal conditions. In arthritis, UPB1112 (n = 5) facilitated the responses to stimulation of knee and ankle, whereas EGLU (n = 5) selectively increased the responses to stimulation of the knee. These data suggest that mGluRs of groups II and III can inhibit nociceptive processing in CeLC neurons. The increased function and endogenous activation of group II mGluRs in the arthritis pain model appear more input-selective than the general changes of group III mGluRs.
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:809360 HCAPLUS
DOCUMENT NUMBER: 145:202709
TITLE: Subchronic administration of LY354740 does not modify ketamine-evoked behavior and neuronal activity in rats
AUTHOR(S): Imre, Gabor; Fokkema, Dirk S.; Ter Horst, Gert J.
CORPORATE SOURCE: Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, 9700 RB, Neth.

SOURCE: European Journal of Pharmacology (2006), 544(1-3), 77-81
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acute treatment with LY354740 {1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate}, a potent and selective agonist for group II metabotropic glutamate receptors (mGlu2/3), has previously been shown to block some schizophrenia-like effects of N-methyl-D-aspartate (NMDA) receptor antagonists, suggesting a novel therapeutic strategy for schizophrenia. The present study examined the effects of subchronic pretreatment with LY354740 (0.3, 3 and 10 mg/kg i.p.) on ketamine-evoked (12 mg/kg s.c.) prepulse inhibition deficits, hyperlocomotion and c-fos expression. At all doses, LY354740 failed to reverse both behavioral and neuronal effects of the ketamine. These results therefore do not support the putative antipsychotic role of LY354740.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:733075 HCAPLUS
DOCUMENT NUMBER: 145:188474

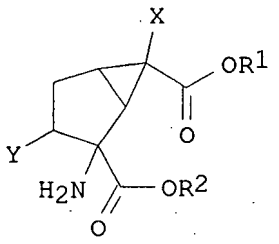
TITLE: Preparation of 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid ester derivatives as group II metabotropic glutamate receptor antagonists

INVENTOR(S): Yasuhara, Akitaka; Sakagami, Kazunari; Ota, Hiroyuki; Nakazato, Atsuro
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 95 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2006193507	A	20060727	JP 2005-330903	20051115
PRIORITY APPLN. INFO.:			JP 2004-363690	A 20041215

OTHER SOURCE(S): MARPAT 145:188474
GI



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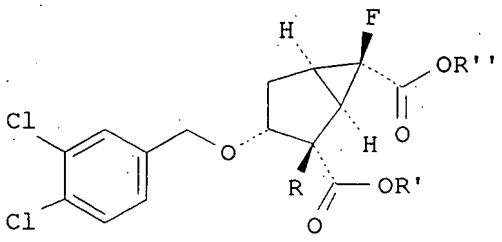


II

AB Title compds. I [R1, R2 = alkyl, alkenyl, alkynyl, etc.; X = H, F; Y = -OCHR3R4, -SR3, -S(O)nR5, etc.; R3, R4 = H, alkyl, alkenyl, etc.; R5 = alkyl, alkenyl, Ph, etc.; n = 1, 2], pharmaceutically acceptable salts or hydrates thereof were prepared For example, reduction of compound II [R = N3; R',
R'' = Et], e.g., prepared from (1R,5R,6R)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylic acid Et ester in 6 steps, followed by hydrolysis using LiOH and SOCl2 mediated esterification with methanol afforded compound II [R = NH2; R' = H; R'' = methyl] hydrochloride. Compound II [R = NH2; R' = H; R'' = methyl] hydrochloride showed antidepressant effects in rat forced swimming test. Compds. I are claimed useful for the treatment of depression.

L9 ANSWER 9 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:537070 HCAPLUS
DOCUMENT NUMBER: 145:159636
TITLE: An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats
AUTHOR(S): Yoshimizu, Takao; Shimazaki, Toshiharu; Ito, Akie; Chaki, Shigeyuki
CORPORATE SOURCE: Psychiatric Diseases and Pain Research, Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, 331-9530, Japan
SOURCE: Psychopharmacology (Berlin, Germany) (2006), 186(4), 587-593
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rationale Abnormalities of glutamatergic neurotransmission have been reportedly observed in psychiatric disorders. Previously, we demonstrated that (1R, 2R, 3R, 5R, 6R)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039) is a selective

antagonist for group II metabotropic glutamate receptors (mGluR2/3), and that it exerted antidepressant effects in some animal behavioral tests. In the present study, we provide addnl. evidence that MGS0039 exhibits antidepressant and anxiolytic effects in exptl. rodent models, which are predictive of clin. efficacy. The learned helplessness (LH) paradigm, which is a common model used to examine the depressive state, was used to assess antidepressant effects of MGS0039. Moreover, anxiolytic effects of MGS0039 were investigated in the conditioned fear stress (CFS) model, which represents emotional abnormality, including anxiety. Results I.p. administration of MGS0039 (10 mg/kg) to rats for 7 days elicited a significant reduction in escape failures in the LH paradigm. In addition, rats treated with MGS0039 (2 mg/kg) showed significantly attenuated freezing behavior in a CFS model, indicating theanxiolytic-like potential of MGS0039. These results suggest that the blockade of mGluR2/3 with MGS0039 may be effective in the treatment of depressive and anxiety disorders.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:447136 HCAPLUS
DOCUMENT NUMBER: 145:89562
TITLE: Prodrugs of 3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039): A potent and orally active group II mGluR antagonist with antidepressant-like potential
AUTHOR(S): Yasuhara, Akito; Nakamura, Masato; Sakagami, Kazunari; Shimazaki, Toshiharu; Yoshikawa, Ryoko; Chaki, Shigeyuki; Ohta, Hiroshi; Nakazato, Atsuro
CORPORATE SOURCE: Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Kita-ku, Saitama-shi, Saitama, 331-9530, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2006), 14(12), 4193-4207
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:89562

AB 3-(3,4-Dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 5 (MGS0039) is a highly selective and potent group II metabotropic glutamate receptor (mGluR) antagonist (antagonist activities for mGluR2; IC50 = 20.0 nM, mGluR3; IC50 = 24.0 nM) and is detected in both plasma (492 ng/mL) and brain (13.2 ng/g) at oral administration of 10 ng/mL [J. Med. Chemical 2004, 47, 4750], but the oral bioavailability of 5 was 10.9%. In order to improve the oral bioavailability of 5, prodrugs of 5 were discovered by esterification of carboxyl group on C6-position of bicyclo[3.1.0]hexane ring. Among these compds., 6-alkyl esters exhibited approx. 10-fold higher concns. of 5 in the plasma and brain of rats after oral administration (e.g., Et ester of 5; plasma, C max = 20.7 ± 1.3 μM) compared to oral administration of 5 (plasma, C max = 2.46 ± 0.62 μM). 3-(3,4-Dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-heptyl ester (7ao), a prodrug of MGS0039, showed antidepressant-like effects in rat forced swimming test and mouse tail suspension test following oral administration. Moreover, following oral administration of 7ao in mice, high concns. of MGS0039 were detected in both the brain and plasma, while

7ao was barely detected. In this paper, we report the synthesis, in vitro metabolic stabilities, and pharmacokinetic profiles of the prodrugs of 5, and the antidepressant-like effects of 7ao.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:352265 HCAPLUS
DOCUMENT NUMBER: 145:306467
TITLE: Modulation of amphetamine-induced dopamine release by group II metabotropic glutamate receptor agonist LY354740 in non-human primates studied with positron emission tomography
AUTHOR(S): van Berckel, Bart N. M.; Kegeles, Lawrence S.; Waterhouse, Rikki; Guo, Ningning; Hwang, Dah-Ren; Huang, Yiyun; Narendran, Rajesh; Van Heertum, Ronald; Laruelle, Marc
CORPORATE SOURCE: Department of Psychiatry, Columbia University, New York, NY, USA
SOURCE: Neuropsychopharmacology (2006), 31(5), 967-977
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pharmacol. evidence suggests that schizophrenia is associated with increased stimulation of dopamine (DA) D2 receptors. Recently, several groups have demonstrated that amphetamine-induced DA release is increased in schizophrenia, providing direct evidence for dysregulation of DA systems in this condition. In healthy volunteers, pretreatment with the noncompetitive N-methyl-D-aspartate (NMDA) antagonist ketamine increases amphetamine-induced DA release to levels similar to those observed in patients with schizophrenia. Therefore, the dysregulation of DA function observed in schizophrenia might be secondary to NMDA hypofunction. In this study, the regulation of this response by glutamate (GLU) transmission was further characterized by using a metabotropic glutamate (mGlu) receptor group II agonist to inhibit GLU transmission. The amphetamine- (0.5 mg/kg i.v.) induced decrease in [11C]raclopride equilibrium-specific binding (V3'') was measured under control conditions and following pretreatment with the mGlu2/3 receptor agonist LY354740 (20 mg/kg i.v.) in four baboons. Amphetamine reduced [11C]raclopride V3'' by 28 ± 7% under control conditions. Following LY354740 pretreatment, amphetamine-induced reduction in [11C]raclopride V3'' was significantly enhanced (35 ± 7%, p=0.002). The enhancement of the amphetamine-induced reduction in [11C]raclopride V3'' by LY354740 was not a simple additive effect, as LY354740 alone did not reduce [11C]raclopride V3''. In conclusion, the results of this study further document the involvement of GLU transmission in regulating the effect of amphetamine-induced DA release, and provide addnl. support to the hypothesis that the dysregulation of DA function revealed by the amphetamine challenge in schizophrenia might stem from a deficit in GLU transmission.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:315080 HCAPLUS
DOCUMENT NUMBER: 145:287
TITLE: Synthesis, in vitro pharmacology, and

structure-activity relationships of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as mGluR2 antagonists

AUTHOR(S): Yasuhara, Akito; Sakagami, Kazunari; Yoshikawa, Ryoko; Chaki, Shigeyuki; Nakamura, Masato; Nakazato, Atsuro

CORPORATE SOURCE: Medicinal Research Laboratories, Ltd, Taisho Pharmaceutical Co., Saitama, 331-9530, Japan

SOURCE: Bioorganic & Medicinal Chemistry (2006), 14(10), 3405-3420
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Chemical modification of the bicyclo[3.1.0]hexane ring C-3 position led to the discovery of 3-alkoxy-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 3-benzylthio-, and 3-benzylamino-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs., metabotropic glutamate receptor 2 (mGluR2) antagonists. In particular, 3-(3,4-dichlorobenzyloxy)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (15ae), (1R,2S,5R,6R)-2-amino-3-(3,4-dichlorobenzylthio)-6-fluorobicyclo[3.1.0]hexane-2,6-carboxylic acid (15at), and (1R,2S,5R,6R)-2-amino-3-(N-(3,4-dichlorobenzylamino))-6-fluorobicyclo[3.1.0]hexane-2,6-carboxylic (15ba) showed high affinity for the mGluR2 receptor (15ae: Ki = 2.51 nM, 15at: Ki = 1.96 nM, and 15ba: Ki = 3.29 nM) and potent antagonist activity for mGluR2 (15ae; IC50 = 34.21 nM, 15at; IC50 = 13.34 nM, and 15ba; IC50 = 35.96 nM). No significant agonist activity for mGluR2 was observed with 15ae, 15at, or 15ba. This paper reports on the synthesis, in vitro pharmacol. profile, and structure-activity relationships (SARs) of 3-substituted-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:220343 HCAPLUS

DOCUMENT NUMBER: 144:403722

TITLE: In vitro and in vivo evaluation of the metabolism and bioavailability of ester prodrugs of MGS0039 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6- dicarboxylic acid), a potent metabotropic glutamate receptor antagonist

AUTHOR(S): Nakamura, Masato; Kawakita, Yasunori; Yasuhara, Akito; Fukasawa, Yoshiki; Yoshida, Koji; Sakagami, Kazunari; Nakazato, Atsuro

CORPORATE SOURCE: Medical Development Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, Japan

SOURCE: Drug Metabolism and Disposition (2006), 34(3), 369-374
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB MGS0039 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid) has been identified as a potent and selective antagonist for metabotropic glutamate

receptors. However, the oral bioavailability of MGS0039 is 10.9% in rats, due to low absorption. Several prodrugs, synthesized to improve absorption, exhibited 40 to 70% bioavailability in rats. This study investigated in vitro metabolism using liver S9 fractions from both cynomolgus monkeys and humans and oral bioavailability in cynomolgus monkeys to select the prodrug most likely to exhibit optimal pharmacokinetic profiles in humans. In monkeys, transformation to active substance was observed (5.9 - 72.8%) in liver S9 fractions, and Bu, n-pentyl, 3-methylbutyl, and 4-methylpentyl ester prodrugs exhibited high transformation ratios (>64%). Cmax levels and F values after oral dosing increased to 4.1- to 6.3-fold and 2.4- to 6.3-fold, resp., and a close relationship between transformation ratios and Cmax and F values was observed, indicating that the hydrolysis rate in liver S9 fractions is the key factor in determining oral bioavailability in monkeys. In humans, n-hexyl, n-heptyl, n-octyl, 5-methylbutyl, and 6-methylpentyl ester prodrugs exhibited high transformation ratios (>65%) in liver S9 fractions. With these prodrugs, n-hexyl, n-heptyl, and 5-methylpentyl ester, almost complete recovery (96 - 99%) was obtained. Given the transformation ratio, we anticipated that the n-heptyl alkyl ester prodrug would exhibit the highest oral bioavailability of active substances in humans, if the hydrolysis rate in liver S9 fractions is indeed the key factor in determining oral bioavailability in humans. On this basis, MGS0210 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid n-heptyl ester) seems to be a promising candidate among MGS0039 prodrugs.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:132700 HCAPLUS
DOCUMENT NUMBER: 144:286568
TITLE: Group-II metabotropic glutamate receptors negatively modulate NMDA transmission at striatal cholinergic terminals: Role of P/Q-type high voltage activated Ca++ channels and endogenous dopamine
AUTHOR(S): Mela, Flora; Marti, Matteo; Fiorentini, Chiara; Missale, Cristina; Morari, Michele
CORPORATE SOURCE: Section of Pharmacology, and Neuroscience Center, Department of Experimental and Clinical Medicine, University of Ferrara, Ferrara, 44100, Italy
SOURCE: Molecular and Cellular Neuroscience (2006), 31(2), 284-292
CODEN: MOCNED; ISSN: 1044-7431
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Striatal cholinergic nerve terminals express functional group-II metabotropic (mGlu) and NMDA glutamate receptors. To investigate whether these receptors interact to regulate ACh release, LY 354740 (a group-II mGlu receptor agonist) and NMDA were co-applied in striatal synaptosomes and slices. LY 354740 prevented the NMDA-evoked [3H]-choline release from synaptosomes and ACh release from slices. In synaptosomes, this modulation was prevented by ω-agatoxin IVA, suggesting that it was mediated by P/Q-type high voltage activated Ca++ channels. In slices, LY 341495 (a group-II mGlu receptor antagonist) enhanced the NMDA-induced ACh release, suggesting that group-II mGlu receptor activation by endogenous glutamate inhibits NMDA transmission. Co-immunopptn. studies excluded

direct group-II mGlu-NMDA receptor interactions. Finally, group-II mGlu neg. modulation of NMDA transmission was abolished in dopamine-depleted synaptosomes and slices, suggesting that it relied on endogenous dopamine. We conclude that group-II mGlu receptors attenuate NMDA inputs at striatal cholinergic terminals via Ca++ channel modulation and dopamine-sensitive pathways.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1351480 HCAPLUS
DOCUMENT NUMBER: 144:81056
TITLE: A metabotropic glutamate 2/3 receptor antagonist, MGS0039, increases extracellular dopamine levels in the nucleus accumbens shell
AUTHOR(S): Karasawa, Jun-ichi; Yoshimizu, Takao; Chaki, Shigeyuki
CORPORATE SOURCE: Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Kita-ku, Saitama, 331-9530, Japan
SOURCE: Neuroscience Letters (2006), 393(2-3), 127-130
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MGS0039, a potent and selective metabotropic glutamate 2/3 (mGlu 2/3) receptor antagonist, exhibits antidepressant-like activities in some animal models. In the present study, the authors examined the effect of MGS0039 on extracellular dopamine levels in the rat nucleus accumbens (NAc) shell using in vivo microdialysis evaluation because accumbal dopamine has been implicated in depression. Local application of MGS0039 into the NAc shell at 10 μM significantly increased extracellular dopamine levels in the NAc shell in freely moving rats. In contrast, local application of 10 μM of LY354740, an mGlu 2/3 receptor agonist, significantly decreased extracellular dopamine levels in the same brain region. These findings suggest that dopamine release in the NAc shell is regulated by mGlu 2/3 receptors, and that the effect on dopamine levels in the NAc shell may partially explain the antidepressant-like properties of mGlu 2/3 receptor antagonists.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1024790 HCAPLUS
DOCUMENT NUMBER: 143:460432
TITLE: An efficient synthesis of LY544344·HCl: a prodrug of mGluR2 agonist LY354740
AUTHOR(S): Coffey, D. Scott; Hawk, Mai Khanh; Pedersen, Steven W.; Vaid, Radhe K.
CORPORATE SOURCE: Lilly Corporate Center, Chemical Product Research and Development, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Tetrahedron Letters (2005), 46(43), 7299-7302
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:460432

AB LY544344·HCl was efficiently prepared in two steps from selective and potent agonist for group II metabotropic glutamate receptors LY354740 as its prodrug. The key step highlighted the in situ masking of the carboxylic acid groups as trimethylsilyl esters to facilitate an effective acylation reaction.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:952560 HCAPLUS
DOCUMENT NUMBER: 143:452105
TITLE: Metabolism and disposition of a potent group II metabotropic glutamate receptor agonist, in rats, dogs, and monkeys
AUTHOR(S): James, Joyce K.; Nakamura, Masato; Nakazato, Atsuro; Zhang, Kanyin E.; Cramer, Merryl; Brunner, Janice; Cook, Jacquelynn; Chen, Weichao G.
CORPORATE SOURCE: Merck Research Laboratories, Merck and Co., Inc., San Diego, CA, USA
SOURCE: Drug Metabolism and Disposition (2005), 33(9), 1373-1381
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Metabolism and disposition of MGS0028 [(1R,2S,5S,6S)-2-amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid monohydrate], a potent group II metabotropic glutamate receptor agonist, were examined in three preclin. species (Sprague-Dawley rats, beagle dogs, and rhesus monkeys). In rats, MGS0028 was widely distributed and primarily excreted in urine as parent and as a single reductive metabolite, identified as the 4R-isomer MGS0034 [(1R,2S,4R,5S,6S)-2-amino-6-fluoro-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid]. MGS0028 had a low brain to plasma ratio at efficacious doses in rats and was eliminated more slowly in rat brain than in plasma. Exposure increased proportionally (1-10 mg/kg p.o.) in rats, with bioavailability >60% at all doses. However, bioavailability was only .apprx.20% in monkeys, and MGS0034 was found in relatively high abundance in plasma. In dogs, oral bioavailability was >60%, and the metabolite was not detected. In vitro metabolism was examined in liver subcellular fractions (microsomes and cytosol) from rat, dog, monkey, and human. Reductive metabolism was observed in rat, monkey, and human liver cytosol incubations, but not in dog liver cytosol incubations. No metabolism of MGS0028 was detected in incubations with liver microsomes from any species. Similar to in vivo results, MGS0028 was reduced in cytosol stereospecifically to MGS0034. The rank order of in vitro metabolite formation (monkey >> rat .apprx. human >> dog) was in agreement with in vivo observations in rats, dogs, and monkeys. Based on the observation of species difference in reductive metabolism, rat and monkey were recommended to be the preclin. species for further characterization prior to testing in humans. Finally, allometric scaling predicts that human pharmacokinetic parameters would be acceptable for further development.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

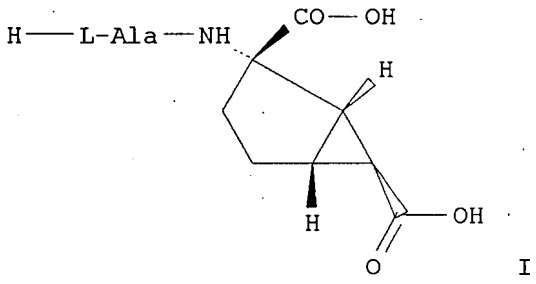
ACCESSION NUMBER: 2005:714957 HCAPLUS
DOCUMENT NUMBER: 144:274498
TITLE: The synthesis of isotopically labeled (+)-2-aminobicyclo[3.1.0]hexane-2,6-carboxylic acid and its 2-oxa- and 2-thia-analogs
AUTHOR(S): Wheeler, William J.; O'Bannon, Douglas D.; Kennedy, Joseph H.; Monn, James A.; Tharp-Taylor, Roger W.; Valli, Matthew J.; Kuo, Fengjiun
CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (2005), 48(8), 605-620
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB As part of a program aimed at the design of conformationally constrained analogs of glutamic acid, (+)-2-aminobicyclo[3.1.0]hexane-2,6-carboxylic acid (I), identified as a highly potent, selective, group II metabotropic glutamate receptor agonist was synthesized and studied clin. Heterocyclic analogs of I were subsequently synthesized in which the C(2) methylene was replaced by an oxygen atom (II) or a sulfur atom (III). Carbon-14-labeled isotopomers of I-III were synthesized to facilitate pre-clin. ADME studies. A tritium-labeled isotopomer of I was also synthesized for use in in vitro expts. A stable labeled isotopomer of rac-I was prepared for use as an internal standard for bioanal. assays. The key step in each of these syntheses was the reaction of 2-oxobicyclo[3.1.0]hexane-6-carboxylic acid (IV) or the appropriate aza or thia compound with K14CN/(NH4)2CO3 using the Bucherer-Berg protocol. In the preparation of the stable labeled isotopomer, rac-IV-[13C2] was prepared in two steps from Et bromoacetate-[UL-13C2]. Subsequent reaction of rac-IV-[13C2] with K13CN/15NH4Cl/Na2CO3, followed by hydrolysis of the hydantoin yielded rac-I-[13C3,15N].

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:609674 HCAPLUS
DOCUMENT NUMBER: 143:241359
TITLE: Dipeptides as Effective Prodrugs of the Unnatural Amino Acid (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (LY354740), a Selective Group II Metabotropic Glutamate Receptor Agonist
AUTHOR(S): Bueno, Ana Belen; Collado, Ivan; De Dios, Alfonso; Dominguez, Carmen; Martin, Jose Alfredo; Martin, Luisa M.; Martinez-Grau, Maria Angeles; Montero, Carlos; Pedregal, Concepcion; Catlow, John; Coffey, D. Scott; Clay, Michael P.; Dantzig, Anne H.; Lindstrom, Terry; Monn, James A.; Jiang, Haiyan; Schoepp, Darryle D.; Stratford, Robert E.; Tabas, Linda B.; Tizzano, Joseph P.; Wright, Rebecca A.; Herin, Marc F.
CORPORATE SOURCE: Lilly, S.A., Madrid, Spain
SOURCE: Journal of Medicinal Chemistry (2005), 48(16), 5305-5320
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:241359
GI



I

AB (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, also known as LY354740, is a highly potent and selective agonist for group II metabotropic glutamate receptors (mGlu receptors 2 and 3) tested in clin. trials. It has been shown to block anxiety in the fear-potentiated startle model. Its relatively low bioavailability in different animal species drove the need for an effective prodrug form that would produce a therapeutic response at lower doses for the treatment of anxiety disorders. The authors have investigated the increase of intestinal absorption of this compound by targeting the human peptide transporter hPepT1 for active transport of di- and tripeptides derived from LY354740. The authors have found that oral administration of an N dipeptide derivative of LY354740 (I) in rats shows up to an 8-fold increase in drug absorption and a 300-fold increase in potency in the fear-potentiated startle model in rats when compared with the parent drug LY354740.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:594734 HCAPLUS
DOCUMENT NUMBER: 143:186915
TITLE: Opposite effects of Zn on the in vitro binding of [3H]LY354740 to recombinant and native metabotropic glutamate 2 and 3 receptors
AUTHOR(S): Malherbe, Pari; Richards, J. Grayson; Broger, Clemens; Zenner, Marie-Therese; Messer, Juerg; Kratzeisen, Claudia; Nakanishi, Shigetada; Mutel, Vincent
CORPORATE SOURCE: Pharma Division, Discovery Research CNS, F. Hoffmann-La Roche Ltd, Basel, Switz.
SOURCE: Journal of Neurochemistry (2005), 94(1), 150-160
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the effect of Zn on agonist binding to both recombinant and native mGlu2 and mGlu3 receptors. Zn had a biphasic

inhibitory effect on recombinant mGlu2 with IC50 values for the high- and low-affinity components of 60±10 μM and 2±0.7 mM, resp. Zn induced a complex biphasic effect of inhibition and enhancement of [3H]LY354740 binding to mGlu3. Observations with a series of chimeric mGlu2/3 receptors suggest that the Zn effect resides in the N-terminal domain of mGlu2 and mGlu3. The authors observed that the His 56 of mGlu2, which corresponds to Asp 63 in mGlu3 was largely accountable for the second phase of the Zn effect. As revealed by quant. receptor radioautog., the addition of up to 100 μM Zn to brain sections of wild-type mice resulted in significant decreases in binding d. in most brain regions. In particular, the mid-mol. layer of the dentate gyrus (DGmol) and the CA1 lacunosum moleculare of hippocampus (CA1-LMol) showed redns. of 62 and 67%, resp. In contrast, the addition of 300 μM Zn to brain sections of mGlu2-/- mice caused large increases in binding d. of 289 and 242% in DGmol and CA1-LMol, resp. Therefore, Zn might play a role as a physiol. modulator of group II mGlu receptor function.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:345343 HCAPLUS
DOCUMENT NUMBER: 143:19260
TITLE: Methyl Substitution of 2-Aminobicyclo[3.1.0]hexane 2,6-Dicarboxylate (LY354740) Determines Functional Activity at Metabotropic Glutamate Receptors: Identification of a Subtype Selective mGlu2 Receptor Agonist
AUTHOR(S): Dominguez, Carmen; Prieto, Lourdes; Valli, Matthew J.; Massey, Steven M.; Bures, Mark; Wright, Rebecca A.; Johnson, Bryan G.; Andis, Sherri L.; Kingston, Ann; Schoepp, Darryle D.; Monn, James A.
CORPORATE SOURCE: Discovery Chemistry and Neuroscience Research Divisions, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(10), 3605-3612
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:19260

AB LY354740 (1) is a highly potent and selective agonist of metabotropic glutamate (mGlu) receptors 2 and 3. In the present study, we have prepared C3- and C4-methyl-substituted variants of rac-1, compds. 5, 9, and 13. Each of these racemic methyl-substituted analogs displaced specific binding of the mGlu2/3 receptor antagonist 3H-2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3-(xanth-9-yl)propanoic acid (3H-LY341495) from membranes expressing mGlu2 or mGlu3 receptor subtypes. Evaluation of the functional effects of this series on second messenger responses in cells expressing human mGlu2 or mGlu3 receptors revealed C3β-Me analog 5 to possess antagonist properties at both mGlu2 and mGlu3 receptors while C4β-Me analog 9 acts as a full agonist at each of these targets. Unexpectedly, we found that incorporation of a Me substituent at the C4α-position as in analog 13 results in a mixed mGlu2 agonist/mGlu3 antagonist pharmacol. profile. All of the mGlu2 agonist and mGlu3 antagonist activity of rac-13 was found to reside in its resolved (+)-isomer.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:309162 HCAPLUS
DOCUMENT NUMBER: 142:456875
TITLE: Anxiolytic-like activity of the mGLU2/3 receptor agonist LY354740 in the elevated plus maze test is disrupted in metabotropic glutamate receptor 2 and 3 knock-out mice
AUTHOR(S): Linden, A.-M.; Shannon, H.; Baez, M.; Yu, J. L.; Koester, A.; Schoepp, D. D.
CORPORATE SOURCE: Neuroscience Research Division, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 284-291
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB (1S,2S,5R,6S)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) is a potent and selective agonist for group II metabotropic glutamate (mGlu2 and mGlu3) receptors, with anxiolytic-like activity in animal and human models, and efficacy in anxiety patients. However, the lack of mGlu2 or mGlu3 receptor specific agonists has prevented in vivo characterization of individual functions of these 2 receptors in mediating the anxiolytic-like effects of LY354740. To utilize mGlu2 receptor and mGlu3 receptor knockout animals and the mGlu2/3 selective antagonist (2S,1'S,2'S)-2-(9-xanthylmethyl)-2-(2'-carboxycyclopropyl)glycine (LY341495) to further investigate the roles of mGlu2 and mGlu3 receptors in mediating the anxiolytic-like actions of LY354740 in a mouse model of anxiety [elevated plus maze (EPM) test]. To confirm that mGlu2/3 receptors are responsible for anxiolytic-like activity in the EPM under these test conditions, mice were pretreated with LY341495 at 30 min prior to s.c. administered LY354740. Subsequently, saline vehicle or LY354740 was administered (s.c.) 30 min before the EPM testing in wild-type, mGlu2 receptor knockout, and mGlu3 receptor knockout mice. LY354740 reduced in a dose-dependent manner anxiety-related behavior on the EPM in wild-type mice with a maximally ED of 10-20 mg/kg s.c. Pretreatment with LY341495 potently prevented the anxiolytic-like effects of LY354740 (20 mg/kg, s.c.) in mice. Although the mGlu2 receptor knockout and mGlu3 receptor knockout mice were grossly normal, the anxiolytic-like activity of LY354740 (20 mg/kg, s.c.) was not evident in either mGlu2 or mGlu3 receptor knockout mice, when compared to their wild-type controls. The activation of both mGlu2 and mGlu3 receptors by LY354740 appears to be required for anxiolytic-like activity in the EPM test in mice. These studies serve as a foundation for addnl. studies on underlying circuits, brain structures, and receptor subtypes involved in the anxiolytic-like actions of mGlu receptor active agents, and the design of future drugs for anxiety disorders in humans.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 23 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:309154 HCAPLUS
DOCUMENT NUMBER: 143:90721

TITLE: Effects of a metabotropic glutamate2/3 receptor agonist (LY544344/LY354740) on panic anxiety induced by cholecystokinin tetrapeptide in healthy humans: preliminary results
AUTHOR(S): Kellner, Michael; Muhtz, Christoph; Stark, Kristina; Yassouridis, Alexander; Arlt, Josef; Wiedemann, Klaus
CORPORATE SOURCE: Department of Psychiatry and Psychotherapy, University Hospital Hamburg-Eppendorf, Hamburg, 20246, Germany
SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 310-315
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Preclin. findings have repeatedly shown an anxiolytic-like action of agonists at metabotropic glutamate receptors type II, such as LY354740. The authors aimed to investigate the effect of LY544344, the prodrug of LY354740, upon exptl. panic anxiety in humans. Twelve healthy human volunteers were treated orally with 80 mg bid LY544344 for 1 wk in a randomized placebo-controlled cross-over study before 50 μg cholecystokinin tetrapeptide (CCK-4) was injected i.v. The authors assessed CCK-induced panic and anxiety symptoms and measured stress hormone release. While no significant treatment effect emerged in the entire sample, a significant reduction of the number of CCK-4-induced panic symptoms and of CCK-4-induced subjective anxiety ratings was detected after removing 2 subjects who did not show decreased CCK-4-elicited ACTH release after LY544344 compared to placebo treatment. Further studies are needed to clarify the potential of LY544344 as a new anxiolytic or antipanic drug.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:309153 HCAPLUS
DOCUMENT NUMBER: 142:475957
TITLE: Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects
AUTHOR(S): Krystal, John H.; Abi-Saab, Walid; Perry, Edward; D'Souza, D. Cyril; Liu, Nianjin; Gueorguieva, Ralitza; McDougall, Lisa; Hunsberger, Tracy; Belger, Aysenil; Levine, Louise; Breier, Alan
CORPORATE SOURCE: Schizophrenia Biological Research Center (116-A), VA Connecticut Healthcare System, West Haven, CT, 06516, USA
SOURCE: Psychopharmacology (Berlin, Germany) (2005), 179(1), 303-309
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Some of the behavioral consequences of deficits in N-methyl-d-aspartate (NMDA) glutamate receptor function are thought to arise from the disinhibition of cortical glutamatergic circuitry. This study evaluated

whether pretreatment with a drug that reduces glutamatergic activation, the group II metabotropic glutamate receptor (mGluR) agonist, LY354740, reduced the cognitive effects of the NMDA glutamate receptor antagonist, ketamine, in healthy human subjects. Nineteen healthy human subjects completed 3 test days during which LY354740 (matched placebo, 100 mg, 400 mg) was administered under double-blind conditions 4 h prior to the single-blind i.v. administration of saline and 5.7 h prior to ketamine administration (bolus of 0.26 mg/kg over 1 min, infusion of 0.65 mg/kg per h for 100 min). Thus on each test day each subject received a single dose of LY354740 (or its matched placebo) and both saline and ketamine infusions. Ketamine impaired attention, working memory, and delayed recall. It also produced pos. and neg. symptoms, perceptual changes, and dysphoric mood. LY354740 did not have a significant effect on working memory on the placebo day; however, it produced a significant dose-related improvement in working memory during ketamine infusion. These data provide preliminary and suggestive evidence that LY354740 or other group II mGluR agonists might play a role in treating working memory impairment related to deficits in NMDA receptor function.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 25 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:298938 HCAPLUS
DOCUMENT NUMBER: 142:423678
TITLE: AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist
AUTHOR(S): Karasawa, Jun-Ichi; Shimazaki, Toshiharu; Kawashima, Naoya; Chaki, Shigeyuki
CORPORATE SOURCE: Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, 331-9530, Japan
SOURCE: Brain Research (2005), 1042(1), 92-98
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB (1R,2R,3R,5R,6R)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039), a selective group II metabotropic glutamate receptor (mGluR) antagonist, exhibits antidepressant-like activities in rodent models. In the present studies, to clarify the involvement of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor activation in exhibition of the antidepressant-like properties of MGS0039, the authors examined the effect of an AMPA receptor antagonist, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoxaline (NBQX), on the antidepressant-like effect of MGS0039 in the mouse tail suspension test. The authors also examined the effects of NBQX on increased serotonin release after treatment with MGS0039 in the rat medial prefrontal cortex (mPFC) using in vivo microdialysis evaluation. In the tail suspension test, MGS0039 (0.3-3 mg/kg, i.p.) treatment dose-dependently and significantly reduced immobility time. Pretreatment with NBQX (10 mg/kg, s.c.) significantly prevented the antidepressant-like effect of MGS0039 in the tail suspension test, while NBQX itself had no effect on immobility time. In the microdialysis evaluation, administration of MGS0039 (10 mg/kg,

i.p.) significantly increased serotonin levels in mPFC in freely moving rats, while NBQX (1 mg/kg, i.p.) itself had no effect on serotonin release in this region. Pretreatment with NBQX significantly attenuated the increase in serotonin release by MGS0039. These findings suggest that stimulation of postsynaptic AMPA receptors plays a role in mediating the pharmacol. effects of MGS0039.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 26 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:234178 HCAPLUS
DOCUMENT NUMBER: 142:367493
TITLE: Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors
AUTHOR(S): Kawashima, Naoya; Karasawa, Jun-ichi; Shimazaki, Toshiharu; Chaki, Shigeyuki; Okuyama, Shigeru; Yasuhara, Akito; Nakazato, Atsuro
CORPORATE SOURCE: Research Strategy Group, Pharmaceutical Business Division, Taisho Pharmaceutical Co., Ltd., Saitama, Saitama, 331-9530, Japan
SOURCE: Neuroscience Letters (2005), 378(3), 131-134
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamatergic abnormalities play roles in several psychiatric disorders. Glutamate acts at two classes of receptors, ionotropic and metabotropic glutamate receptors (mGluR), the latter is classified into three group, based on receptor homol. and signaling mechanisms. Among them, recent pharmacol. and histochem. studies suggest that the group II mGluR (mGluR2 and mGluR3) plays crucial roles in the control of emotional states. We previously reported that MGS0039, a selective group II mGluR antagonist, exhibited dose-dependent antidepressant-like effects in some animal models. However, the mechanism by which group II mGluR antagonists exhibit such effects is still unclear. In the present two studies, we examined neuropharmacol. effects of group II mGluR antagonists on monoaminergic neurons. In an electrophysiol. study, MGS0039 dose-dependently and significantly increased the firing rate of dorsal raphe nucleus (DRN) serotonergic neurons. LY341495, another group II mGluR antagonist, also increased DRN serotonergic neural activity significantly. Consistent with the findings of this electrophysiol. study, MGS0039 significantly increased extracellular level of serotonin in rat medial prefrontal cortex in a microdialysis study. In contrast, MGS0039 had no effect on the activity of locus coeruleus noradrenergic neurons. These findings suggest that modulation of serotonergic neuron might be, at least in part, responsible for the antidepressant-like effects of group II mGluR antagonists.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:133442 HCAPLUS
DOCUMENT NUMBER: 142:255021
TITLE: Sprouting of mossy fibers and presynaptic inhibition by group II metabotropic glutamate receptors in pilocarpine-treated rat

hippocampal slice cultures
AUTHOR(S): Thomas, A. M.; Corona-Morales, A. A.; Ferraguti, F.; Capogna, M.
CORPORATE SOURCE: Medical Research Council, Anatomical Neuropharmacology Unit, Oxford, OX1 3TH, UK
SOURCE: Neuroscience (Oxford, United Kingdom) (2005), 131(2), 303-320
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mossy fiber sprouting (MFS) is a phenomenon observed in the epileptic hippocampus. We have studied MFS, in 7, 14 and 21 day in vitro (DIV) organotypic slice cultures, or in slice cultures treated with pilocarpine (0.5 mM) or pilocarpine and atropine (0.1 mM or 0.5 mM) for 48-72 h at 5 DIV and tested at 21 DIV. Acute application of pilocarpine directly activated hilar neurons and elicited epileptic-like discharges in CA3 pyramids and mossy cells of 5-8 DIV cultures, without causing substantial cell death, as assessed by lactate dehydrogenase measurements. Timm staining revealed increases in MFS in chronic pilocarpine-treated cultures, which was prevented by prior application of atropine. Extracellular synaptic responses were recorded in the granule cell layer and elicited by antidromic mossy fiber stimulation. The GABAA antagonist 6-imino-3-(4-methoxyphenyl)-1(6H)-pyridazinebutanoic acid (1 μM) induced a greater increase in the coastline bursting index in pilocarpine-treated cultures than in 21 DIV controls. However, there was no significant increase in the frequency of spontaneous or miniature synaptic events recorded in granule cells from pilocarpine-treated cultures. Granule cells were filled with biocytin and morphometric anal. revealed that the length of axon collaterals in the granule and mol. layer was longer in pilocarpine-treated cultures than in 21 DIV controls. Dual recordings between granule cells and between granule and hilar neurons showed that pilocarpine-treated cultures had a larger proportion of monosynaptic and polysynaptic connections. The group II metabotropic glutamate receptor (mGluR) agonist LY 354740 (0.5 μM) suppressed excitatory but not inhibitory monosynaptic currents. LY 354740 also inhibited antidromically evoked action currents in granule cells from pilocarpine- and to a lesser extent in pilocarpine and atropine-treated cultures, suggesting that group II mGluRs can reside along the axon and suppress action potential invasion. We provide direct evidence for the development of functional MFS and suggest a novel, axonal mechanism by which presynaptic group II mGluRs can inhibit selected synapses.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

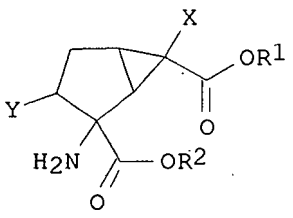
L9 ANSWER 28 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:14355 HCAPLUS
DOCUMENT NUMBER: 142:113634
TITLE: Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esters as Group II metabotropic glutamate receptor antagonists
INVENTOR(S): Yasuhara, Akito; Sakagami, Kazunari; Ohta, Hiroshi; Nakazato, Atsuro
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 144 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000791	A1	20050106	WO 2004-JP9398	20040625
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004252017	A1	20050106	AU 2004-252017	20040625
CA 2530706	A1	20050106	CA 2004-2530706	20040625
EP 1637517	A1	20060322	EP 2004-746867	20040625
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1812960	A	20060802	CN 2004-80017917	20040625
BR 2004011823	A	20060808	BR 2004-11823	20040625
US 2007021394	A1	20070125	US 2004-562018	20040625
MX 2005PA13740	A	20060517	MX 2005-PA13740	20051215
IN 2005CN03529	A	20070525	IN 2005-CN3529	20051226
NO 2006000428	A	20060310	NO 2006-428	20060126

PRIORITY APPLN. INFO.:
JP 2003-181930 A 20030626
JP 2003-373511 A 20031031
JP 2004-128663 A 20040423
WO 2004-JP9398 W 20040625

OTHER SOURCE(S): MARPAT 142:113634
GI



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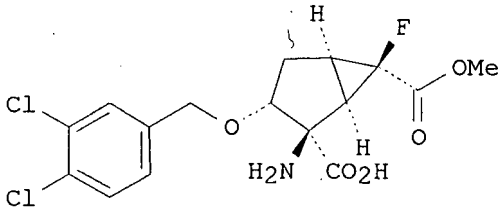


II

AB The title compds. I [wherein R1 and R2 = independently alkyl, alkenyl, alkynyl, etc.; X = H or F; Y = (un)substituted alkoxy, SH, amino, etc.] or hydrates or pharmaceutically acceptable salts thereof are prepared as Group II metabotropic glutamate receptor antagonists. For example, the compound II was prepared in a multi-step synthesis. II showed antagonistic effect on Group II metabotropic glutamate receptor in rat. I are useful for the

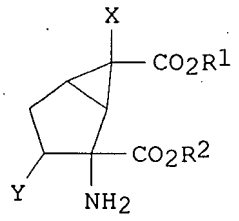
treatment of schizophrenia, anxiety, and diseases related to these, i.e., psychiatrical disorders such as depression, bipolar disorder, and epilepsy (no data).

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 29 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:14354 HCAPLUS
DOCUMENT NUMBER: 142:113754
TITLE: Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as antagonists of group II metabotropic glutamate receptor
INVENTOR(S): Yasuhara, Akito; Sakagami, Kazunari; Ohta, Hiroshi; Nakazato, Atsuro
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000790	A1	20050106	WO 2004-JP9384	20040625
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2006142388	A1	20060629	US 2005-562010	20051223
PRIORITY APPLN. INFO.:			JP 2003-181931	A 20030626
			WO 2004-JP9384	W 20040625

OTHER SOURCE(S): MARPAT 142:113754
GI



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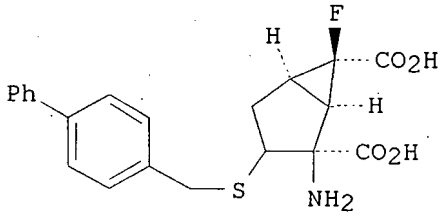


II

AB The title compds. [I; R1, R2 = H, C1-10 alkyl, Ph, naphthyl, mono- or diphenyl-C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, hydroxy-C2-10 alkyl,

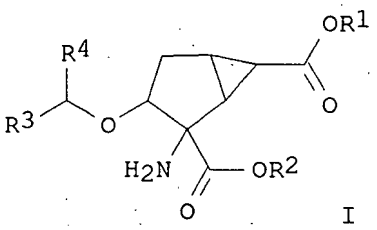
C1-10 alkoxycarbonyl-C1-10 alkyl, amino-C2-10 alkyl, C1-10 alkoxy-C1-10 alkyl; X = H, F; Y = NH2, SR3, S(O)nR7, SCHR3R4, S(O)nCHR3R4, NHCHR3R4, N(CHR3R4)(CHR5R6), NHCOR3, O2CR7; wherein R3-R6 = H, C1-10 alkyl, (un)substituted Ph, naphthyl, 1-7 halogen(s)-substituted naphthyl, heteroaryl; R7 = C1-10 alkyl, (un)substituted Ph, naphthyl, 1-7 halogen(s)-substituted naphthyl, heteroaryl; n = 1,2], pharmaceutically acceptable salts thereof, or hydrates of either are prepared These compds., e.g. (II), had an antagonistic effect on a Group II metabotropic glutamate receptor with IC50 of ≤200 nM, and are effective in treatments for and prevention of psychiatric disorders and neurol. diseases.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

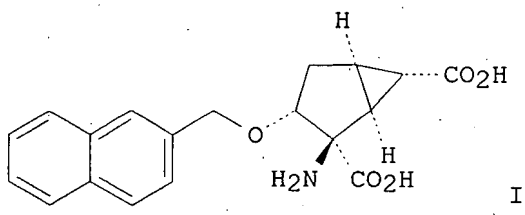
L9 ANSWER 30 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:14353 HCAPLUS
DOCUMENT NUMBER: 142:113633
TITLE: Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esters as Group II metabotropic glutamate receptor antagonists
INVENTOR(S): Yasuhara, Akito; Sakagami, Kazunari; Ohta, Hiroshi; Nakazato, Atsuro
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000789	A1	20050106	WO 2004-JP9365	20040625
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2007063129	A	20070315	JP 2003-181932	20030626
PRIORITY APPLN. INFO.:			JP 2003-181932	A 20030626
OTHER SOURCE(S):	MARPAT 142:113633			

GI



I



II

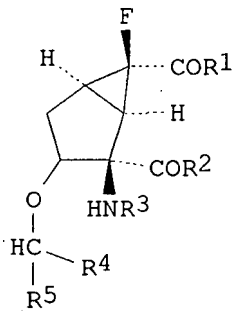
AB The title compds. I [wherein R1 and R2 = independently H, alkyl, Ph, etc.; R3 = Naphthyl or (un)substituted Ph; R4 = H, alkyl, naphthyl, or (un)substituted Ph] or hydrates or pharmaceutically acceptable salts thereof are prepared as Group II metabotropic glutamate receptor antagonists. For example, the compound II was prepared in a multi-step synthesis. II showed antagonistic effect on Group II metabotropic glutamate receptor with IC50 of 4.27 nM in cow. I are useful for the treatment of schizophrenia, anxiety, and diseases related to these, i.e., psychiatrical disorders such as depression, bipolar disorder, and epilepsy (no data).

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1038326 HCAPLUS
DOCUMENT NUMBER: 142:16843
TITLE: mGluR2 antagonists and 2-amino-3-alkoxy-6-[3.1.0]hexan-2,6-dicarboxylate derivatives for treatment of nervous system diseases
INVENTOR(S): Nakazato, Atsuro; Taki, Shigeyuki; Sakagami, Kazunari; Dean, Reiko; Ota, Hiroyuki; Hirota, Shiho; Yasuhara, Akitaka
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 70 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004339199	A	20041202	JP 2004-86153	20040324
PRIORITY APPLN. INFO.:			JP 2003-117907 A	20030423

OTHER SOURCE(S): MARPAT 142:16843
GI



I

AB The antidepressant mGlur2 antagonists and 2-amino-3-alkoxy-6-[3.1.0]hexan-2,6-dicarboxylate derivs., salts, and hydrates are claimed for treatment of nervous system diseases, including bipolar affective disorder, psychiatry disorder, anxiety, epilepsy, drug dependence, cognition disorder, Alzheimer's disease, Huntington's disease, Parkinson disease, muscle stiffness, brain ischemia, spinal cord injury, head injury, etc.

L9 ANSWER 32 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:947580 HCAPLUS
DOCUMENT NUMBER:	142:17500
TITLE:	Activation of Group II and Group III metabotropic glutamate receptors by endogenous ligand(s) and the modulation of synaptic transmission in the superficial superior colliculus
AUTHOR(S):	Thompson, H.; Neale, S. A.; Salt, T. E.
CORPORATE SOURCE:	Division of Visual Science, Institute of Ophthalmology, University College London, London, EC1V 9EL, UK
SOURCE:	Neuropharmacology (2004), 47(6), 822-832 CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER:	Elsevier B.V.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Previous work from this laboratory indicates that Group II/III metabotropic glutamate (mGlu) receptors modulate responses of SC neurons to visual stimuli in vivo. It is thought that tonic levels of glutamate may be sufficient to activate some mGlu receptors. The authors wished to investigate if these receptors are activated under ambient conditions in SC. Field excitatory postsynaptic potentials (fEPSPs) evoked by optic tract stimulation were recorded from 300 μm slices of the adult pigmented rat superior colliculus at 34°. The Group II receptor selective agonist LY354740 (100-300 nM) had no significant effect on the peak amplitude of the fEPSP, although it did enhance the late phase of the fEPSP. To test for activation of Group II receptors by endogenous ligand, the selective antagonists LY341495 (50 nM) or EGLU (200 μM) were applied: these either enhanced or reduced the fEPSP amplitude. In similar expts. carried out at 22°, no effect was seen. The fEPSP enhancements, but not the fEPSP redns., could be occluded by GABA antagonists. Application of higher concns. of LY341495 (300, 600 nM-known to also affect Group III receptors, particularly mGlu8), or co-application of 50 nM LY341495 and the Group III-selective antagonist CPPG (100 μM) produced enhancements of responses, or counteracted response redns. over

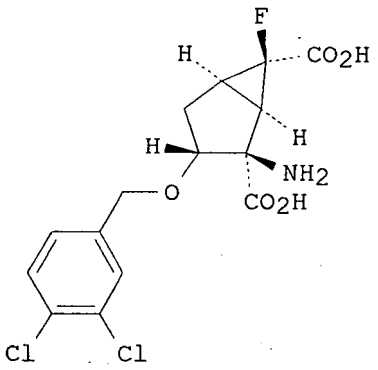
those seen with 50 nM LY341495 alone. The predominant Group II receptor in SC is mGlu3. It is known that this can be located presynaptically on GABAergic and glutamatergic terminals, postsynaptically, and on glia. The authors' results indicate that such receptors are tonically activated by endogenous transmitter, have distinct effects, and influence retino-collicular transmission. Furthermore, there is a segregation of effects where receptors exert some of their effects via modulation of GABAergic circuitry.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

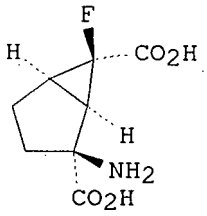
L9 ANSWER 33 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:814656 HCAPLUS
DOCUMENT NUMBER: 141:325597
TITLE: Anxiolytic-like activity of MGS0039, a potent group II metabotropic glutamate receptor antagonist, in a marble-burying behavior test
AUTHOR(S): Shimazaki, Toshiharu; Iijima, Michihiko; Chaki, Shigeyuki
CORPORATE SOURCE: Psychiatric Diseases and Pain Research, Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, Saitama, 331-9530, Japan
SOURCE: European Journal of Pharmacology (2004), 501(1-3), 121-125
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamatergic abnormalities are involved in several psychiatric disorders. Clin. evidence demonstrates altered glutamatergic neurotransmission in patients suffering from obsessive-compulsive disorder. MGS0039, (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, is a novel group II metabotropic glutamate (mGlu) receptor antagonist. We examined MGS0039's potential anti-obsessive-compulsive disorder activity, using the marble-burying behavior test as a model of obsessive-compulsive disorder. MGS0039 as well as LY341495 ((2S,1'S,2'S)-2-(9-xanthylmethyl)-2-(2'-carboxycycloprolyl)glycine), another group II mGlu receptor antagonist, inhibited marble-burying behavior. We also demonstrated that this effect was significantly attenuated by a group II mGlu receptor agonist. This data indicates that group II mGlu receptor antagonists may exert anti-obsessive-compulsive disorder effects in clin. use.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 34 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:620394 HCAPLUS
DOCUMENT NUMBER: 141:243074
TITLE: Synthesis, in vitro pharmacology, structure-activity relationships, and pharmacokinetics of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent and selective group II metabotropic glutamate receptor antagonists
AUTHOR(S): Nakazato, Atsuro; Sakagami, Kazunari; Yasuhara, Akito;

Ohta, Hiroshi; Yoshikawa, Ryoko; Itoh, Manabu; Nakamura, Masato; Chaki, Shigeyuki
CORPORATE SOURCE: Medicinal Chemistry Laboratory, Taisho Pharmaceutical Co. Ltd., Kita-ku, Saitama-shi, Saitama, 331-9530, Japan
SOURCE: Journal of Medicinal Chemistry (2004), 47(18), 4570-4587
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:243074
GI



I



II

AB Group II metabotropic glutamate receptor (mGluR) antagonists, 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs., e.g., I, were discovered by the incorporation of a hydroxy or alkoxyl group onto the C-3 portion of selective and potent group II mGluR agonist II. Among these compds., I (MGS0039) was a highly selective and potent group II mGluR antagonist with the best pharmacokinetic profile. I exhibited high affinities for mGlu 2 (Ki = 2.38 ± 0.40 nM) and mGlu 3 (4.46 ± 0.31 nM) but low affinity for mGluR 7 (Ki = 664 ± 106 nM), and potent antagonist activities for mGlu 2 (IC50 = 20.0 ± 3.67nM) and mGluR 3 (IC50 = 24.0 ± 3.54 nM) but much less potent antagonist activities for mGlu 4 (IC50 = 1740 ± 1080 nM), mGlu 6 (IC50 = 2060 ± 1270 nM), mGlu 1 (IC50 = 93300 ± 14600 nM), and mGluR 5 (IC50 = 117000 ± 38600 nM). No significant agonist activities of I were found for mGluRs 2, 3, 4, 6, 1, and 5 (EC50 > 100000 nM). Furthermore, I exhibited dose-dependent oral absorption (plasma Cmax: 214 ± 56.7, 932 ± 235, and 2960 ± 1150 ng/mL for 3 mg/kg, 10 mg/kg, and 30 mg/kg, po, resp.) and acceptable blood-brain barrier penetration (brain Cmax: 13.2 ng/mL for 10 mg/kg, po 6 h). The synthesis, in vitro pharmacol. profile, and structure-activity relationships of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs., and pharmacokinetic profiles of several typical compds, are presented.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 35 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:602541 HCAPLUS
DOCUMENT NUMBER: 141:200322
TITLE: Closed state of both binding domains of homodimeric mGlu receptors is required for full activity
AUTHOR(S): Kniazeff, Julie; Bessis, Anne-Sophie; Maurel, Damien; Ansanay, Herve; Prezeau, Laurent; Pin, Jean-Philippe
CORPORATE SOURCE: Laboratory of Functional Genomics, Department of Molecular Pharmacology, Centre National de la Recherche Scientifique, Montpellier, 34094, Fr.
SOURCE: Nature Structural & Molecular Biology (2004), 11(8), 706-713
CODEN: NSMBCU; ISSN: 1545-9993
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Membrane receptors, key components in signal transduction, often function as dimers. These include some G protein-coupled receptors such as metabotropic glutamate (mGlu) receptors that have large extracellular domains (ECDs) where agonists bind. How agonist binding in dimeric ECDs activates the effector domains remains largely unknown. The structure of the dimeric ECDs of mGlu1 solved in the presence of agonist revealed two specific conformations in which either one or both protomers are in an agonist-stabilized closed form. Here the authors examined whether both conformations correspond to an active form of the full-length receptor. Using a system that allows the formation of dimers made of a wild-type and a mutant subunit, the authors show that the closure of one ECD per dimer is sufficient to activate the receptor, but the closure of both ECDs is required for full activity.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 36 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:307137 HCAPLUS
DOCUMENT NUMBER: 141:1681
TITLE: Pharmacological manipulation of mGlu2 receptors influences cognitive performance in the rodent
AUTHOR(S): Higgins, Guy A.; Ballard, Theresa M.; Kew, James N. C.; Grayson Richards, J.; Kemp, John A.; Adam, Geo; Woltering, Thomas; Nakanishi, Shigetada; Mutel, Vincent
CORPORATE SOURCE: Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Neuropharmacology (2004), 46(7), 907-917
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Atrophy of the medial temporal lobes, including the glutamatergic cortical-hippocampal circuitry, is an early event in Alzheimer's disease (AD) and probably contributes to the characteristic short-term mnemonic decline. Pharmacol. strategies directly targeted to ameliorating this functional decline may represent a novel approach for the symptomatic treatment of AD. Presynaptic group II metabotropic glutamate receptors (i.e., mGlu2 and mGlu3) exert a powerful modulatory influence on the function of these pathways, in

particular the perforant pathway. Using a combination of mGlu2 receptor knockout mice and the group II agonist LY354740, the authors show that activation of mGlu2 receptors produces a cognitive impairment, i.e., a delay-dependent deficit in delayed matching and non-matching to position, and impaired spatial learning in a Morris water maze. Conversely, a group II antagonist, LY341495, improved acquisition of spatial learning. LY354740 potently reduced field excitatory postsynaptic potentials in hippocampal slices from wild type but not mGlu2 receptor knockout mice. Taken together, these results suggest that activation of mGlu2 receptors evokes a powerful inhibitory effect on hippocampal synaptic transmission and mGlu2 agonists produce a cognitive deficit consistent with this change. Conversely, mGlu2 receptor antagonists may improve certain aspects of cognition and thus represent a novel approach for the symptomatic treatment of AD.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 37 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:252341 HCAPLUS
DOCUMENT NUMBER: 140:264522
TITLE: Metabotropic glutamate receptor (mGluR) antagonist-based methods for treating disorders associated with mGluRs, including addiction and depression
INVENTOR(S): Markou, Athina; Kenny, Paul; Paterson, Neil; Semenova, Svetlana
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH; The Scripps Research Institute
SOURCE: PCT Int. Appl., 156 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024150	A2	20040325	WO 2003-EP10061	20030910
WO 2004024150	A3	20040819		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW				
RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
CA 2498022	A1	20040325	CA 2003-2498022	20030910
AU 2003270166	A1	20040430	AU 2003-270166	20030910
EP 1539149	A2	20050615	EP 2003-750512	20030910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003014192	A	20050726	BR 2003-14192	20030910
CN 1694701	A	20051109	CN 2003-825021	20030910
JP 2006501265	T	20060112	JP 2004-535478	20030910
US 2006148835	A1	20060706	US 2005-527525	20051014

PRIORITY APPLN. INFO.: US 2002-409867P P 20020910
WO 2003-EP10061 W 20030910

AB Methods are provided for treating disorders associated with mGluRs by simultaneously inhibiting at least two mGluRs belonging to at least two different groups. In one embodiment, methods are provided for treating a disorder associated with mGlu receptors 2, 3, and 5, including administering to a subject in need thereof an effective amount of at least one antagonist which modulates mGluR2, mGluR3, and mGluRS. The disorders treated by the method include e.g. nicotine addiction, cocaine addiction, and depression. Compds. used in the invention include e.g. 2-methyl-6-(phenylethynyl)pyridine.

L9 ANSWER 38 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:131733 HCAPLUS
DOCUMENT NUMBER: 141:218747
TITLE: Anxiolytic Activity of the MGLU2/3 Receptor Agonist LY354740 on the Elevated Plus Maze is Associated with the Suppression of Stress-Induced c-Fos in the Hippocampus and Increases in c-Fos Induction in Several Other Stress-Sensitive Brain Regions
AUTHOR(S): Linden, A-M.; Greene, S. J.; Bergeron, M.; Schoepp, D. D.
CORPORATE SOURCE: Lilly Research Laboratories, Neuroscience Research Division, Eli Lilly and Company, Indianapolis, IN, USA
SOURCE: Neuropsychopharmacology (2004), 29(3), 502-513
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY354740 is a potent and selective agonist for group II metabotropic glutamate (mGlu) receptors, mGlu2 and mGlu3 receptors, with anxiolytic activity in several animal models of anxiety, including the elevated plus maze (EPM) test. Here, we studied neuronal activation in mouse brain after EPM exposure in saline- and LY354740-treated mice using c-Fos immunoreactivity as a marker. The effect of LY354740 on c-Fos expression was also studied in cage control (no EPM) mice. Pretreatment with LY354740 (20 mg/kg, s.c.) produced robust anxiolytic behavior on the EPM. LY354740 administration decreased EPM-induced increases in c-Fos expression in the CA3 of the hippocampus, while having no significant effects on basal c-Fos expression in the hippocampus. LY354740 administration significantly increased c-Fos expression in specific limbic regions, including the lateral division of the central nucleus of the amygdala (CeL), lateral parabrachial nucleus, locus coeruleus, and Edinger-Westphal nucleus, whether or not animals were exposed to the EPM. Moreover, LY354740 administration per se significantly increased c-Fos expression in regions processing sensory information, including the paraventricular and lateral geniculate nucleus of the thalamus as well as the nucleus of the optic tract and superior colliculus. In particular, the suppression of fear-evoked neuronal activity in the hippocampus and drug-induced increases in neuronal activation in the CeL have been previously linked to the anxiolytic effects of clin. effective drugs such as benzodiazepines, and thus may contribute to anxiolytic actions of LY354740 in animal models and human anxiety patients.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 39 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:126085 HCAPLUS
DOCUMENT NUMBER: 141:82129
TITLE: MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity
AUTHOR(S): Chaki, Shigeyuki; Yoshikawa, Ryoko; Hirota, Shiho; Shimazaki, Toshiharu; Maeda, Maoko; Kawashima, Naoya; Yoshimizu, Takao; Yasuhara, Akito; Sakagami, Kazunari; Okuyama, Shigeru; Nakanishi, Shigetada; Nakazato, Atsuro
CORPORATE SOURCE: Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, 331-9530, Japan
SOURCE: Neuropharmacology (2004), 46(4), 457-467
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study describes the pharmacol. profile of (1R,2R,3R,5R,6R)-2-Amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039), a novel group II mGluR antagonist. MGS0039 showed high affinity for both mGluR2 (Ki = 2.2 nM) and mGluR3 (Ki = 4.5 nM), which are comparable to LY341495, another group II mGluR antagonist. MGS0039 attenuated both glutamate-induced inhibition of forskolin-evoked cAMP formation in CHO cells expressing mGluR2 (IC50 = 20 nM) or mGluR3 (IC50=24 nM) and glutamate-increased [35S]GTPγS binding to mGluR2 (pA2=8.2), which means that MGS0039 acts as an antagonist. MGS0039 shifted the dose-response curve of glutamate-increased [35S]GTPγS binding rightward without altering the maximal response, and thereby indicating competitive antagonism. MGS0039 showed no significant effects on other mGluRs as well as the other receptors and transporters we studied. MGS0039 (0.3-3 mg/kg, i.p.) as well as LY341495 (0.1-3 mg/kg, i.p.) had dose-dependent antidepressant-like effects in the rat forced swim test and in the mouse tail suspension test. In contrast, MGS0039 (0.3-3 mg/kg, i.p.) had no apparent effect in the rat social interaction test and in the rat elevated plus-maze. These results indicate that MGS0039 is a potent and selective antagonist of group II mGluR, and that group II mGluR antagonists, like MGS0039, have an antidepressant-like potential in exptl. animal models.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 40 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:96754 HCAPLUS
DOCUMENT NUMBER: 140:368470
TITLE: Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039
AUTHOR(S): Yoshimizu, Takao; Chaki, Shigeyuki
CORPORATE SOURCE: Medicinal Research Laboratories, Medicinal Pharmacology Laboratory, Psychiatric Diseases and Pain Research, Taisho Pharmaceutical Co., Ltd., Kita-ku, Saitama, 331-9530, Japan
SOURCE: Biochemical and Biophysical Research Communications (2004), 315(2), 493-496
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have previously reported that MGS0039, a novel antagonist of group II metabotropic glutamate receptors (mGluRs), exerts antidepressant-like effects in exptl. animal models. Recent studies suggest that the behavioral effects of chronic antidepressant treatment are mediated by the stimulation of neurogenesis in the hippocampus. In the present study, we examined the effects of MGS0039 on cell proliferation in the adult mouse hippocampus. MGS0039 (5 or 10 mg/kg) or fluvoxamine was administered chronically to male ICR mice over a period of 14 days. Multiple bromodeoxyuridine (BrdU) administrations were performed after the last drug injection to label dividing cells. Immunohistochem. analyses after BrdU injections revealed that chronic MGS0039 treatment enhanced BrdU-pos. cells in the dentate gyrus (.apprx.62% increase) in the same manner as chronic fluvoxamine treatment. This is the first in vivo study to demonstrate an increase in cell proliferation following a blockade of group II mGluRs. These findings raise the possibility that MGS0039 may exert antidepressant-like effects by modulating cell proliferation in the hippocampus.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 41 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:41259 HCAPLUS
DOCUMENT NUMBER: 140:94299
TITLE: Preparation of prodrugs of excitatory amino acids
INVENTOR(S): Monn, James Allen; Pedregal-Tercero, Concepcion; Blanco-Urgoiti, Jaime Gonzalo
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004706	A1	20040115	WO 2003-IB2826	20030623
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003242924	A1	20040123	AU 2003-242924	20030623
PRIORITY APPLN. INFO.:			EP 2002-380151 A	20020705
			US 2002-413589P P	20020925
			WO 2003-IB2826 W	20030623

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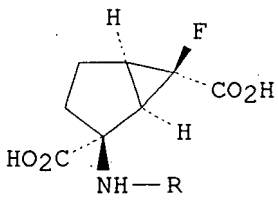

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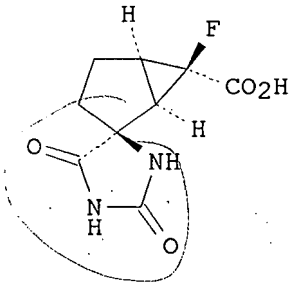

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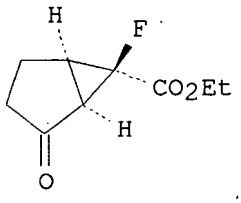

III

AB The invention relates to a synthetic excitatory amino acid prodrug I (R = L-alanyl), including processes for its preparation and use in the treatment of neurol. disorders and psychiatric disorders. The synthesis includes hydrolysis of spirohydantoin derivative II, which is obtained by cyclization reaction of 2-oxobicyclo[3.1.0]hexane derivative III with (NH4)2CO3 and KCN.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 42 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:40907 HCAPLUS

DOCUMENT NUMBER: 140:210576

TITLE: The mGlu2/3 receptor agonist, LY354740, blocks immobilization-induced increases in noradrenaline and dopamine release in the rat medial prefrontal cortex

AUTHOR(S): Swanson, Chad J.; Perry, Kenneth W.; Schoepp, Darryle D.

CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

SOURCE: Journal of Neurochemistry (2004), 88(1), 194-202
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The metabotropic glutamate (mGlu2/3) receptor agonist, LY354740, exhibits anxiolytic-like properties in a number of rodent models. The present study utilized in vivo microdialysis to examine the effects of LY354740 on extracellular monoamine levels in the medial prefrontal cortex (mPFC) of animals subjected to 30 min immobilization stress. Immobilization stress significantly elevated extracellular levels of noradrenaline (NA) and dopamine (DA) in the mPFC, while systemic administration of LY354740 (30 mg/kg, s.c.) significantly attenuated immobilization-induced increases in both NA and DA. Reverse-dialysis of LY354740 (30 μM) into the mPFC significantly attenuated immobilization-induced increases in NA, but not DA without affecting basal levels of either amine. In sep. studies in the presence of citalopram (1 μM; reverse dialysis into the mPFC), systemic administration of LY354740 attenuated immobilization-induced increases in NA and DA, but had no effect on serotonin (5-HT) levels.

Co-administration of the selective mGlu2/3 receptor antagonist, LY341495, partially or fully reversed the attenuation in NA and DA levels produced by LY354740, resp. Taken together, these data suggest that LY354740 may produce anti-stress actions, in part, by blocking stress-related increases in catecholamines in the mPFC via mGlu2/3 receptor stimulation.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 43 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:991499 HCAPLUS
DOCUMENT NUMBER: 140:42463
TITLE: Preparation of prodrugs of excitatory amino acids
INVENTOR(S): Moher, Eric David; Monn, James Allen; Pedregal-Tercero, Concepcion
PATENT ASSIGNEE(S): Eli Lilly and Company, USA; Collado, Cano Ivan; Blanco-Urgoiti, Jamie Gonzalo
SOURCE: PCT Int. Appl., 172 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104217	A2	20031218	WO 2003-US15405	20030606
WO 2003104217	A3	20040226		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2488167	A1	20031218	CA 2003-2488167	20030606
AU 2003232146	A1	20031222	AU 2003-232146	20030606
EP 1517915	A2	20050330	EP 2003-757266	20030606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006503807	T	20060202	JP 2004-511287	20030606
BR 2003011558	A	20070427	BR 2003-11558	20030606
US 2005222231	A1	20051006	US 2004-516559	20041130
IN 2004KN01838	A	20060721	IN 2004-KN1838	20041202
MX 2004PA12518	A	20050217	MX 2004-PA12518	20041210
NO 2005000122	A	20050110	NO 2005-122	20050110

PRIORITY APPLN. INFO.:	EP 2002-380120	A	20020611
	EP 2002-380121	A	20020611
	US 2002-415936P	P	20021003
	US 2002-415937P	P	20021003
	WO 2003-US15405	W	20030606

OTHER SOURCE(S): MARPAT 140:42463
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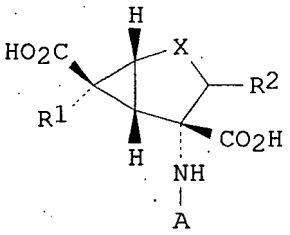

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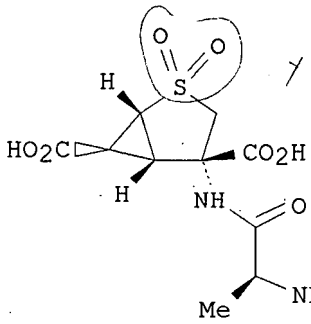

II

AB The invention relates to synthetic excitatory amino acid prodrugs for the treatment of neurol. disorders and psychiatric disorders. Bicyclic amino acids I [A is H-Q1-10, where Q is aminoacyl; X is O, S, SO, SO2, or substituted methylene; R1 is H or F; R2 is H, F, or OH] or their pharmaceutically-acceptable salts are claimed. Thus, prodrug II.HCl was prepared via peptide coupling reaction and shown to exhibit comparable concentration in rat plasma to that of the non-prodrug form.

L9 ANSWER 44 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:818322 HCAPLUS
DOCUMENT NUMBER: 139:302068
TITLE: Therapy for psychoses combining an atypical antipsychotic and an mGlu2/3 receptor agonist
INVENTOR(S): Johnson, Bryan Glenn; Schoepp, Darryle Darwin
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003084610	A1	20031016	WO 2003-US7283	20030321
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2478227	A1	20031016	CA 2003-2478227	20030321
AU 2003218063	A1	20031020	AU 2003-218063	20030321
EP 1492595	A1	20050105	EP 2003-714045	20030321
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005528378	T	20050922	JP 2003-581846	20030321
US 2005192273	A1	20050901	US 2004-509772	20040928
PRIORITY APPLN. INFO.:			US 2002-369771P	P 20020403
			US 2002-369797P	P 20020403

WO 2003-US7283 W 20030321

AB The invention provides a pharmaceutical composition and methods for treating psychosis comprising the combination or a first component which is an atypical antipsychotic with a second component which is a mGlu2/3 receptor agonist. The invention also provides a pharmaceutical composition and method of treating a psychiatric disorder comprising the combination of a first component which is an atypical antipsychotic with a second component which is a compound which allosterically enhances receptor activity for mGlu2 and/or mGlu3.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 45 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:701954 HCAPLUS

DOCUMENT NUMBER: 139:302181

TITLE: The second intracellular loop of metabotropic glutamate receptors recognizes C termini of G-protein α-subunits

AUTHOR(S): Havlickova, Michaela; Blahos, Jaroslav; Brabet, Isabelle; Liu, Jianfeng; Hruskova, Bohdana; Prezeau, Laurent; Pin, Jean-Philippe

CORPORATE SOURCE: Institute of Experimental Medicine, Department of Molecular Pharmacology, Czech Academy of Science, Prague, 142 20, Czech Rep.

SOURCE: Journal of Biological Chemistry (2003), 278(37), 35063-35070
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Heptahelical receptor coupling selectivity to G-proteins is controlled by a large contact area that involves several portions of the receptor and each subunit of the G-protein. In the G-protein α subunit, the C-terminal 5 residues, the N terminus, and the αN-β1 and α4-α5 loops play important roles. On the receptor side, both the second and third (i2 and i3) intracellular loops as well as the C-terminal tail probably contact these different regions of the G-protein. It is now accepted that the C terminus of the α subunit binds in a cavity formed by the i2 and i3 loops. Among the various G-protein-coupled receptors (GPCRs), class III receptors that include metabotropic glutamate (mGlu) receptors greatly differ from the rhodopsin-like GPCRs, but the contact zone between these receptors and the G-protein is less understood. The C terminus of the α subunit has been shown to play a pivotal role in the selective recognition of class III GPCRs. Indeed, the mGlu2 and mGlu4 and -8 receptors can discriminate between α subunits that differ at the level of their C-terminal end only (such as Gqo and Gqz). Here, the authors examine the role of the i2 loop of mGluRs in the selective recognition of this region of the α subunit. To that aim, the authors analyzed the coupling properties of mGlu2 and mGlu4 or -8 receptors and chimeras containing the i2 loop of the converse receptor to G-protein α subunits that only differ by their C termini (Gqo,Gqz, and their point mutants). The authors' data demonstrate that the central portion of the i2 loop is responsible for the selective recognition of the C-terminal end of the α subunit, especially the residue on position -4. These data are consistent with the proposal that the C-terminal end of the G-protein α subunit interacts with residues in a cavity formed by

the i2 and i3 loops in class III GPCRs, as reported for class I GPCRs.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 46 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:683260 HCAPLUS
DOCUMENT NUMBER: 140:70874
TITLE: Group II metabotropic and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate glutamate receptors regulate the deficit in brain reward function associated with nicotine withdrawal in rats
AUTHOR(S): Kenny, Paul J.; Gasparini, Fabrizio; Markou, Athina
CORPORATE SOURCE: Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 306(3), 1068-1076
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study investigated the role of ionotropic and metabotropic glutamate receptors in the deficits in brain reward function, as measured by elevations in intracranial self-stimulation (ICSS) reward thresholds, associated with nicotine withdrawal. The group II metabotropic glutamate (mGlull) receptor agonist LY314582 [a racemic mixture of LY354740 ([+]-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid) (2.5 - 7.5 mg/kg)] precipitated withdrawal-like elevations in ICSS thresholds, a sensitive measure of reward function, in nicotine-dependent but not control rats. LY314582 did not affect response latencies, a measure of performance in the ICSS paradigm. Bilateral microinfusion of LY314582 (10 - 100 ng/side) into the ventral tegmental area likewise precipitated dose-dependent threshold elevations in nicotine-dependent rats. Furthermore, a single injection of the mGlull receptor antagonist LY341495 (2S-2-amino-2-[1S,2S-2-carboxycyclopropan-1-yl]-3-[xanth-9-yl]propionic acid) (1 mg/kg) attenuated the threshold elevations observed in rats undergoing spontaneous nicotine withdrawal. MGlull receptors are primarily located on glutamatergic terminals throughout the mesocorticolimbic system, where they act as inhibitory autoreceptors. To investigate whether mGlull receptors contributed to nicotine withdrawal by decreasing glutamatergic transmission, we next examined whether direct blockade of postsynaptic glutamate receptors precipitated withdrawal-like reward deficits in nicotine-dependent rats. The α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoxaline (NBQX; 0.01 - 1 mg/kg) precipitated withdrawal-like threshold elevations in nicotine-dependent but not control rats, whereas 6-methyl-2-[phenylethynyl]-pyridine (MPEP; 0.01-3 mg/kg) and dizocilpine (MK-801; 0.01 - 0.2 mg/kg), antagonists at metabotropic glutamate 5 and N-methyl-D-aspartate receptors, resp., did not. Overall, these data demonstrate that mGlull receptors play an important role in the reward deficits associated with nicotine withdrawal. Furthermore, it is likely that mGlull receptors generate this reward deficit, at least in part, by decreasing glutamate transmission at AMPA/kainate receptors.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 47 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:669206 HCAPLUS
DOCUMENT NUMBER: 139:391600
TITLE: Functional calcium coupling with the human metabotropic glutamate receptor subtypes 2 and 4 by stable co-expression with a calcium pathway facilitating G-protein chimera in Chinese hamster ovary cells
AUTHOR(S): Kowal, Dianne; Nawoschik, Stanley; Ochalski, Rafal; Dunlop, John
CORPORATE SOURCE: Neuroscience Discovery Research, Wyeth Research, Princeton, NJ, 08543, USA
SOURCE: Biochemical Pharmacology (2003), 66(5), 785-790
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of the current study was to facilitate functional calcium assays, compatible with the fluorometric imaging plate reader platform, for the human metabotropic glutamate receptor (mGluR) subtypes 2 and 4, by co-expressing each receptor with a G-protein chimera comprising Gαq with the C-terminal five amino acids replaced with those from Gαi3 (GqGi3). Transfection of GqGi3 into previously validated stable CHO cell lines expressing mGluR2 or mGluR4 allowed for the selection of new double transfectants in which application of L-glutamate and other mGluR agonists resulted in calcium coupling with a high signal:noise ratio (maximal changes in relative fluorescence units up to 20,000). The rank order of agonist potency for the stimulation of calcium mobilization in the mGluR2/GqGi3 stable cell line was LY354740>L-CCG-I=DCG-IV>L-glutamate≥(2R,4R)-APDC≥(1S,3R)-ACPD. In the mGluR4/GqGi3 stable cell line the rank order of agonist potency was L-AP4>L-SOP≥ACPT-I=L-CCG-I≥L-glutamate=(R,S)-PPG. By comparison, equivalent potency orders and a significant correlation in functional activities were observed when the same compds. were profiled in [35S]GTPγS binding assays for each mGluR subtype. These results validate the use of functional calcium assays, amenable to high-throughput applications on the fluorometric imaging plate reader, for the mGluR2 and mGluR4 subtypes when co-expressed in stable cell lines with the GqGi3 chimera.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 48 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:601382 HCAPLUS
DOCUMENT NUMBER: 140:122575
TITLE: Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans
AUTHOR(S): Grillon, Christian; Cordova, Jeremy; Levine, Louise R.; Morgan, Charles A., III
CORPORATE SOURCE: Mood and Anxiety Disorder Program, NIMH/NIH/DHHS, MSC 2670, Bethesda, MD, 20892-2670, USA
SOURCE: Psychopharmacology (Berlin, Germany) (2003), 168(4), 446-454
CODEN: PSCHDL; ISSN: 0033-3158

PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY354740, a structural analog of glutamate that shows specificity at the mGluR2/3 receptor, has anxiolytic effects in animal models. This study investigated the anxiolytic effects of LY354740 in humans using the fear-potentiated startle reflex methodol. Subjects were given either placebo (n=16), 20 mg LY354740 (n=15), or 200 mg LY354740 (n=13). The fear-potentiated startle tests examined startle potentiation to shock anticipation and to darkness. Consistent with previous results, startle was increased by threat of shock and by darkness. LY354740 did not affect baseline startle. Correspondingly, subjects did not report LY354740 to be sedative. LY354740 significantly reduced the increase in startle magnitude during shock anticipation, but not during darkness. Subjective reports of state anxiety and neg. affectivity during the fear-potentiated startle tests were also reduced in a dose-dependent manner by LY354740. These results suggest that LY354740 has an anxiolytic profile in humans without being sedative.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 49 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:591035 HCAPLUS
DOCUMENT NUMBER: 139:143973
TITLE: 6-Fluorobicyclo[3.1.0]hexane derivatives
INVENTOR(S): Nakazato, Atsuro; Chaki, Shigeyuki; Sakagami, Kazunari; Dean, Ryoko; Ohta, Hiroshi; Hirota, Shiho; Yasuhara, Akito
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co.,ltd., Japan
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003061698	A1	20030731	WO 2002-JP13693	20021226
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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CA 2471642	A1	20030731	CA 2002-2471642	20021226
EP 1459765	A1	20040922	EP 2002-793421	20021226
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BR 2002015462	A	20041130	BR 2002-15462	20021226
CN 1610557	A	20050427	CN 2002-826388	20021226
US 2005119345	A1	20050602	US 2003-500101	20021226
ZA 2005002085	A	20050629	ZA 2005-2085	20021226

HU 200402649	A2	20051028	HU 2004-2649		20021226
NZ 533699	A	20060526	NZ 2002-533699		20021226
NO 2004002530	A	20040922	NO 2004-2530		20040616
ZA 2004004795	A	20050617	ZA 2004-4795		20040617
IN 2004CN01417	A	20060210	IN 2004-CN1417		20040623
MX 2004PA06322	A	20041004	MX 2004-PA6322		20040625
US 7157594	B2	20070102	US 2005-500101		20050204
HK 1073258	A1	20070323	HK 2005-106035		20050715
PRIORITY APPLN. INFO.:			JP 2001-395797	A	20011227
			WO 2002-JP13693	W	20021226

OTHER SOURCE(S): MARPAT 139:143973
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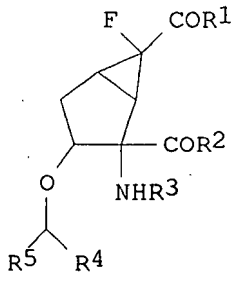

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AB Antidepressants containing as the active ingredient compds. having group II metabotropic glutamate receptor antagonism; and 2-amino-3-alkoxy-6-fluorobicyclo[3.1.0]- hexane-2,6-dicarboxylic acid derivs. represented by the general formula [I], pharmaceutically acceptable salts thereof, or hydrates of the salts: I wherein R1 and R2 may be the same or different from each other and are each hydroxyl, C1-10 alkoxy, or the like; R3 is C1-10 acyl, C1-6 alkoxy-C1-6 acyl, or the like; and R4 and R5 may be the same or different from each other and are each hydrogen, C1-10 alkyl, or the like.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 50 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:567563 HCAPLUS
DOCUMENT NUMBER: 140:12895
TITLE: Antipsychotic action of selective group II metabotropic glutamate receptor agonist MGS0008 and MGS0028 on conditioned avoidance responses in the rat
AUTHOR(S): Takamori, Kazuaki; Hirota, Shiho; Chaki, Shigeyuki; Tanaka, Makoto
CORPORATE SOURCE: Research Management Section, Medicinal Research Laboratories, Taisho Pharmaceutical Co. Ltd., Saitama, 330-8530, Japan
SOURCE: Life Sciences (2003), 73(13), 1721-1728
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study was designed to investigate the antipsychotic-like

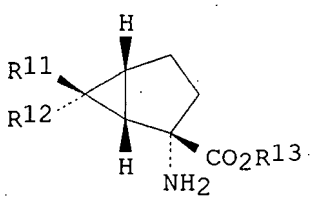
effects of selective group II metabotropic glutamate receptor (mGluR) agonists, 5-{2-[4-(6-fluoro-1H-indole-3-yl) piperidin-1-yl]ethyl}-4-(4-fluorophenyl)thiazole-2-carboxylic acid amide (MGS0008) and (1R, 2S, 5S, 6S)-2-amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid monohydrate (MGS0028) on conditioned avoidance responses in rats. MGS0008 (1, 3 and 10 mg/kg, p.o.) and MGS0028 (0.3, 1 and 3 mg/kg, p.o.) significantly and reduced conditioned avoidance responses in a dose-dependent fashion. Similar effects were seen with LY418426 (0.3, 1 and 3 mg/kg, p.o.), but not with LY354740 (3, 10 and 30 mg/kg, p.o.), both of which are selective agonists for group II mGluR. Since this effect is seen with a wide range of antipsychotics, such as haloperidol and clozapine [Life Sciences 71 (2002) 947], group II mGluR agonists deserve further attention for possible antipsychotic activity.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 51 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:551486 HCAPLUS
DOCUMENT NUMBER: 139:101417
TITLE: Preparation of prodrugs of excitatory amino acids
INVENTOR(S): Bueno Melendo, Ana Belen; De Dios, Alfonso; Dominguez-Fernandez, Carmen; Ferritto Crespo, Rafael; Herin, Marc; Martin, Jose Alfredo; Martinez-Grau, Maria Angeles; Massey, Steven Marc; Monn, James Allen; Pedregal-Tercero, Concepcion; Valli, Matthew John
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057661	A1	20030717	WO 2002-US36145	20021205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002361611	A1	20030724	AU 2002-361611	20021205
EP 1458671	A1	20040922	EP 2002-797089	20021205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2005009912	A1	20050113	US 2004-496716	20040526
PRIORITY APPLN. INFO.:			EP 2001-500291	A 20011221
			WO 2002-US36145	W 20021205

OTHER SOURCE(S): MARPAT 139:101417
GI



I

AB Bicyclic amino acids I [R11 is CO2R14 and R12 is H or F; or R11 is H or F and R12 is CO2R14; R13, R14 are H (not both H), heterocyclylalkyl, or arylalkyl] or their pharmaceutically-acceptable salts were prepared for use as modulators of metabotropic glutamate receptor function. The invention further relates to pharmaceutical compns. for the treatment of neurol. disorders and psychiatric disorders. Thus, (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-(2-methoxybenzyl ester) (II, claimed compound) was prepared from the the diacid via esterification of the N-allyloxycarbonyl-protected oxazolidinone derivative, followed by deprotection. Rat plasma concns. of compds. of the invention were compared with those of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) (4887 ng/mL for II, vs. 466 ng/mL for LY354740).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 52 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:485801 HCAPLUS
DOCUMENT NUMBER: 139:245691
TITLE: Stereocontrolled synthesis of a potent agonist of group II metabotropic glutamate receptors, (+)-LY354740, and its related derivatives
AUTHOR(S): Ohfune, Yasufumi; Demura, Takashi; Iwama, Seiji; Matsuda, Hiromi; Namba, Kosuke; Shimamoto, Keiko; Shinada, Tetsuro
CORPORATE SOURCE: Graduate School of Science, Department of Material Science, Osaka City University, Sugimoto, Osaka, 558-8585, Japan
SOURCE: Tetrahedron Letters (2003), 44(29), 5431-5434
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:245691

AB Efficient synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) and its structurally related analogs has been accomplished starting with (1S,2R)-1-amino-2-hydroxycyclopentane- or cyclohexanecarboxylic acid via an intramol. cyclopropanation of α-diazo acetamide.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 53 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:232954 HCAPLUS

DOCUMENT NUMBER: 138:367015
TITLE: Dopaminergic hyperactivity in striatum in schizophrenia: a failure of cortical glutaminergic control?
AUTHOR(S): Kegeles, Lawrence S.; Laruelle, Marc
CORPORATE SOURCE: Departments of Psychiatry and Radiology, Columbia University, New York, NY, 10032, USA
SOURCE: Advances in Behavioral Biology (2002), 53(Catecholamine Research), 427-430
CODEN: ADBBBW; ISSN: 0099-6246
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of D2 receptor imaging studies that support an underlying glutaminergic regulatory dysfunction is presented. The scans were combined with pharmacol. disruption of cortical-subcortical glutamatergic regulation in healthy volunteers and in nonhuman primates. Two agents were used, the noncompetitive N-methyl-d-aspartate-glutamate receptor antagonist ketamine, and the group II metabotropic glutamate receptor agonist LY354740. It was shown that acute i.v. ketamine administration enhances amphetamine-stimulated dopamine transmission, and does so to a degree similar to the exaggerated response to amphetamine alone previously reported in patients with schizophrenia. Acute disruption of glutamatergic transmission appears to provide a pharmacol. model of the striatal dopaminergic hyperactivity found in schizophrenia.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 54 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:168835 HCAPLUS
DOCUMENT NUMBER: 138:188078
TITLE: Preparation of amino acid conjugates as agonists or antagonists, for a metabotropic glutamate receptor or a NAALADase enzyme for therapeutic uses
INVENTOR(S): Kozikowski, Alan P.; Wroblewski, Jarda T.; Nan, Fajun
PATENT ASSIGNEE(S): Georgetown University, USA
SOURCE: U.S., 69 pp., Cont.-in-part of U.S. Ser. No. 559,978.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6528499	B1	20030304	US 2000-662767	20000915
US 6479470	B1	20021112	US 2000-559978	20000427
WO 2002022627	A2	20020321	WO 2001-US28923	20010914
WO 2002022627	A3	20020704		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001091001	A5	20020326	AU 2001-91001	20010914
US 2004002478	A1	20040101	US 2003-374765	20030225
PRIORITY APPLN. INFO.:			US 2000-559978	A2 20000427
			US 1999-131627P	P 19990428
			US 1999-166915P	P 19991122
			US 2000-188031P	P 20000309
			US 2000-662767	A 20000915
			WO 2001-US28923	W 20010914

AB Title compds. [G-W-Z(G)-Y]2X, [where X = CO, CS, SO2, CR(OR), or CR(SR); Y = (CR2)n, (NR)n, or a bond; Z = CR, C(NR2) or C(NH-acyl); W = (CR2)m, (NR)m, or a bond; G = H, CO2H, SO3H, P(O)(OH)2, SR, or 2-R-tetrazol-5-yl; R = H, alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, or neg. charge when R is bonded to a heteroatom; m, n = independently 0-3; and their stereo isomers and mixts.] were prepared for use as metabotropic glutamate receptor modulators (agonists or antagonists) or NAALADase inhibitors in treating disease involving ischemia. Thus, dibenzyl L-glutamate tosylate was reacted with triphosgene to give the tetrabenzyl ester ureido compound, which was deesterified to give N,N'-carbonyldi-L-glutamic acid (FN11). In vivo antitumor tests using U-87 glioblastoma xenograft showed that FN11 reduced tumor volume to a value of .apprx.0.4-0.6 (at 10 or 100 μM) after 4 days treatment, and .apprx. 1.0 (at both dosages) after 7 days treatment. The antiangiogenesis activity of FN11 was examined with similarly grown tumors, and revealed a preponderance of avascular and low vascular areas in tumors treated with FN11 at 100 μM. Studies of neuroprotective properties of FN compds. revealed that none were quite as effective as the control compound tested.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 55 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2003:161469 HCAPLUS
DOCUMENT NUMBER:	138:280655
TITLE:	LY-354740 Eli Lilly
AUTHOR(S):	Pilc, Andrzej
CORPORATE SOURCE:	Institute of Pharmacology, Polish Academy of Sciences, Krakow, 31-343, Pol.
SOURCE:	IDrugs (2003), 6(1), 66-71 CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER:	PharmaPress Ltd.
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review. Lilly is developing LY-354740, the lead compound in a series of derivs. of the metabotropic glutamate receptor group II agonist L-CCG-1, for the potential treatment of anxiety.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

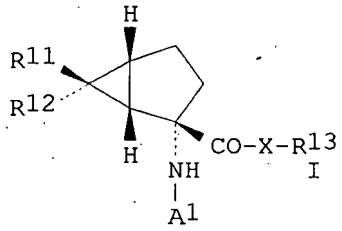
L9 ANSWER 56 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2003:58111 HCAPLUS
DOCUMENT NUMBER:	138:122858
TITLE:	Preparation of prodrugs of excitatory amino acids
INVENTOR(S):	Bueno Melendo, Ana Belen; De Dios, Alfonso; Dominguez-Fernandez, Carmen; Ferritto Crespo, Rafael; Herin, Marc; Martin, Jose Alfredo; Martin-Cabrejas,

Luisa Maria; Martinez-Grau, Maria Angeles; Massey, Steven Marc; Monn, James Allen; Montero Salgado, Carlos; Pedregal-Tercero, Concepcion; Valli, Matthew John
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006489	A2	20030123	WO 2002-US19825	20020702
WO 2003006489	A3	20030925		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002345789	A1	20030129	AU 2002-345789	20020702
EP 1423411	A2	20040602	EP 2002-744537	20020702
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004176459	A1	20040909	US 2003-480517	20031210
PRIORITY APPLN. INFO.:			EP 2001-500175 A	20010709
			EP 2001-500275 A	20011123
			WO 2002-US19825 W	20020702

OTHER SOURCE(S): MARPAT 138:122858
GI



AB Bicyclic amino acids I [R11 is CO-Y-R14 and R12 is H or F; or R11 is H or F and R12 is CO-Y-R14; R13, R14 are H, alkyl, alkenyl, alkynyl, or aryl; A1 is H or aminoacyl; X, Y are O or aminoacyl, provided that when X is O, Y is not O] or their pharmaceutically-acceptable salts were prepared for use as modulators of metabotropic glutamate receptor function. The invention further relates to methods of

using, and pharmaceutical compns. comprising, the compds. for the treatment of neurol. disorders and psychiatric disorders. Thus, (1S,2S,5R,6S)-2-amino-2-[(1'S)-carboxy-3'-methylbutyl]carbamoylbicyclo[3.1.0]hexane-6-carboxylic acid (II) was prepared via coupling of (1S,2S,5R,6S)-2-(allyloxycarbonylamino)bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-allyl ester with L-leucine allyl ester hydrochloride, followed by deprotection. Rat plasma concns. of compds. of the invention were compared with those of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) (1248 ng/mL for II, vs. 466 ng/mL for LY354740).

L9 ANSWER 57 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:27739 HCAPLUS
DOCUMENT NUMBER: 139:30608
TITLE: The mGluR5 antagonist MPEP, but not the mGluR2/3 agonist LY314582, augments PCP effects on prepulse inhibition and locomotor activity
AUTHOR(S): Henry, S. A.; Lehmann-Masten, V.; Gasparini, F.; Geyer, M. A.; Markou, A.
CORPORATE SOURCE: Departments of Neurosciences and Psychiatry, University of California, San Diego, La Jolla, CA, 92093, USA
SOURCE: Neuropharmacology (2003), Volume Date 2002, 43(8), 1199-1209
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phencyclidine (PCP), a non-competitive antagonist of ionotropic N-methyl-D-aspartate (NMDA) receptors, produces psychotomimetic effects, such as a disruption in prepulse inhibition (PPI) of the startle response. NMDA antagonists also induce locomotor hyperactivity in rodents. We hypothesized that, like NMDA receptors, metabotropic glutamate receptors (mGluRs) modulate PPI and locomotor activity either alone or, in the case of mGluR5, via interaction with NMDA receptors. Rats treated with the mGluR5 antagonist MPEP (2-methyl-6-phenylethynylpyridine) or the mGluR2/3 agonist LY314582, either alone or in combination with PCP, were tested in PPI and locomotor activity paradigms. Neither MPEP nor LY314582 altered PPI. MPEP, but not LY314582, potentiated the PPI-disruptive effects of PCP. MPEP alone did not alter locomotor or exploratory behavior, but augmented the complex, time-dependent locomotor-stimulating effects of PCP. LY314582 dose-dependently decreased locomotor activity and exploratory holepokes. LY314582 did not alter the PCP-induced increases in locomotor activity, but further decreased the number of holepokes. The effects of MPEP on the response to PCP may reflect the cooperation and co-localization of NMDA and mGlu5 receptors.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 58 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:973357 HCAPLUS
DOCUMENT NUMBER: 138:232050
TITLE: Group II metabotropic glutamate receptors within the amygdala regulate fear as assessed with potentiated startle in rats
AUTHOR(S): Walker, David L.; Rattiner, Lisa M.; Davis, Michael

CORPORATE SOURCE: Emory University School of Medicine, USA
SOURCE: Behavioral Neuroscience (2002), 116(6), 1075-1083
CODEN: BENEDJ; ISSN: 0735-7044
PUBLISHER: American Psychological Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The contribution to fear and fear learning of amygdala Group II metabotropic glutamate receptors was examined in rats. Pretest infra-amygdala infusions of the Group II receptor agonist LY354740 (0.3 or 1.0 μg/side) significantly disrupted fear-potentiated startle. The same rats were unimpaired when later tested without drug. The Group II receptor agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (3.0 μg/side) mimicked the effect of LY354740, and coadministration of the Group II receptor antagonist LY341495 (0.3 μg/side) prevented it. Pretraining LY354740 (0.3 μg/side) infusions also blocked learning. The effects on learning and performance were significantly less pronounced in rats with misplaced cannulas. Thus, Group II metabotropic receptors within or very near the amygdala regulate fear and fear learning and are a potential target for anxiolytic compds.

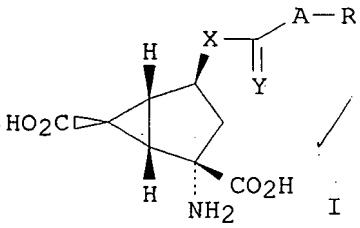
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 59 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:675985 HCAPLUS
DOCUMENT NUMBER: 137:201606
TITLE: Preparation of bicyclic excitatory amino acid derivatives
INVENTOR(S): Massey, Steven Marc; Monn, James Allen; Prieto, Lourdes; Valli, Matthew John
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068380	A1	20020906	WO 2002-US1247	20020212
WO 2002068380	A8	20050623		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002239938	A1	20020912	AU 2002-239938	20020212
EP 1370519	A1	20031217	EP 2002-705812	20020212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004116489	A1	20040617	US 2003-467429	20031208
PRIORITY APPLN. INFO.:			US 2001-270512P	P 20010222

US 2001-340607P P 20011030
WO 2002-US1247 W 20020212

OTHER SOURCE(S): MARPAT 137:201606
GI



I

AB Bicyclic amino acids I [X = CH2, O, NH; Y = O, S, N, H2; A = a bond, O, N, C1-10 alkyl, C2-10 alkenyl or alkynyl, (un)substituted aryl, heterocyclyl or the group XC(:Y)AR is 2-benzoxazolylmethyl, 2-benzothiazolylmethyl, or 2-benzimidazolylmethyl] or their pharmaceutically-acceptable salts were prepared as modulators of metabotropic glutamate receptor function and are useful in the treatment of neurol. and psychiatric disorders. Thus, (1S*,2S*,4S*,5R*,6S*)-2-amino-4-[3-(3-chlorophenyl)ureido]bicyclo[3.1.0]hexane-2,6-dicarboxylic acid [I; XC(:Y)AR = 3-(3-chlorophenyl)ureido] (claimed compound) was prepared by treatment of (1S*,2S*,4S*,5R*,6S*)-2-[(tert-butoxycarbonyl)amino]-4-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid di-Et ester (preparation given) with 3-chlorophenyl isocyanate in CH2Cl2 and then HCl gas in EtOAc. Compds. of the invention have improved affinity for the mGlu3 receptors when compared to compds. of United States patent 5,958,960.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 60 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:539648 HCAPLUS
DOCUMENT NUMBER: 137:94005
TITLE: Preparation of prodrugs of excitatory amino acids
INVENTOR(S): Coffey, David Scott; Dantzig, Anne Hollins; Hillgren, Kathleen Michele; Massey, Steven Marc; Moher, Eric David; Monn, James Allen; Pedersen, Steven Wayne; Sweetana, Stephanie Ann; Valli, Matthew John; Bueno Melendo, Ana Belen; De Dios, Alfonso; Dominguez-Fernandez, Carmen; Herin, Marc F.; Martin-Cabrejas, Luisa Maria; Martin, Jose Alfredo; Martinez-Grau, Maria Angeles; Montero Salgado, Carlos; Pedregal-Tercero, Concepcion
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

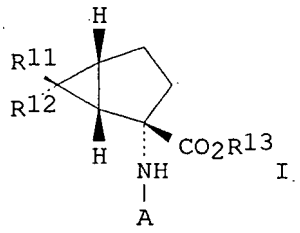
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002055485	A1	20020718	WO 2002-US488		20020109
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1310482	A1	20030514	EP 2001-500264		20011107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
AU 2002241827	A1	20020724	AU 2002-241827		20020109
EP 1351925	A1	20031015	EP 2002-707416		20020109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2004138304	A1	20040715	US 2004-465972		20040126
US 7038077	B2	20060502			

PRIORITY APPLN. INFO.:	EP 2001-500008	A	20010111
	EP 2001-500208	A	20010802
	US 2001-329789P	P	20011016
	US 2001-361644P	P	20011022
	EP 2001-500264	A	20011107
	WO 2002-US488	W	20020109

OTHER SOURCE(S): MARPAT 137:94005

GI



I

AB Bicyclic amino acids I [R11 is CO2R14 and R12 is H or F; or R11 is H or F and R12 is CO2R14; R13, R14 = H, C1-C10 alkyl, C2-C4 alkenyl, aryl or arylalkyl; A is (Q)p, p = 1-10 and Q is aminoacyl; provided that the compound is not one in which R11 is CO2R14, R12, R13 and R14 are H, p is 1, and Q is L-alanyl] or their pharmaceutically acceptable salts were prepared for use as modulators of metabotropic glutamate receptor function. The invention further relates to methods of using, and pharmaceutical compns. comprising, the compds. for the treatment of neurol. disorders and psychiatric disorders. Thus, (1S,2S,5R,6S)-2-[[2(S)-aminopropionyl]amino]bicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride (II) was prepared via coupling reaction of N-(tert-butoxycarbonyl)-L-alanine, followed by deprotection. Rat plasma concns. of compds. of the invention were compared with those of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) (7114 ng/mL for II, vs. 466 ng/mL for LY354740).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

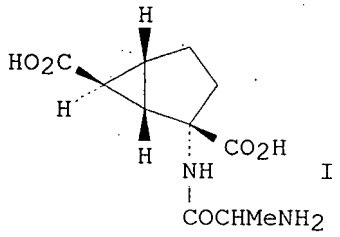
L9 ANSWER 61 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:539644 HCAPLUS
DOCUMENT NUMBER: 137:94004
TITLE: Preparation of prodrugs of excitatory amino acids
INVENTOR(S): Bueno Melendo, Ana Belen; Coffey, David Scott; Dantzig, Anne Hollins; De Dios, Alfonso; Dominguez-Fernandez, Carmen; Herin, Marc; Hillgren, Kathleen Michele; Martin, Jose Alfredo; Martin-Cabrejas, Luisa Maria; Martinez-Grau, Maria Angeles; Massey, Steven Marc; Moher, Eric David; Monn, James Allen; Montero Salgado, Carlos; Pedersen, Steven Wayne; Pedregal-Tercero, Concepcion; Sweetana, Stephanie Ann; Valli, Matthew John
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055481	A1	20020718	WO 2001-US45866	20011221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1310480	A1	20030514	EP 2001-500263	20011107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2433667	A1	20020718	CA 2001-2433667	20011214
HU 200400620	A2	20041228	HU 2004-620	20011214
NZ 526050	A	20050324	NZ 2001-526050	20011214
AU 2002228737	A1	20020724	AU 2002-228737	20011221
AU 2002228737	B2	20070104		
EP 1368304	A1	20031210	EP 2001-989859	20011221
EP 1368304	B1	20070307		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016770	A	20031223	BR 2001-16770	20011221
JP 2004524292	T	20040812	JP 2002-556156	20011221
AT 356111	T	20070315	AT 2001-989859	20011221
IN 2003KN00643	A	20050311	IN 2003-KN643	20030519
ZA 2003004351	A	20040903	ZA 2003-4351	20030603
NO 2003003166	A	20030909	NO 2003-3166	20030710
MX 2003PA06186	A	20040213	MX 2003-PA6186	20030710
US 2004121962	A1	20040624	US 2003-250448	20031112

PRIORITY APPLN. INFO.:

EP 2001-500007	A	20010111
EP 2001-500206	A	20010802
US 2001-329786P	P	20011016
EP 2001-500263	A	20011107
WO 2001-US45866	W	20011221

OTHER SOURCE(S): MARPAT 137:94004
GI



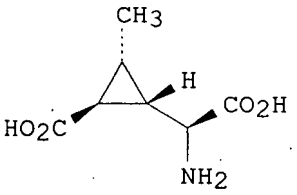
I

AB Bicyclic amino acid I and its pharmaceutically acceptable salts were prepared for use as modulators of metabotropic glutamate receptor function. The invention further relates to methods of using, and pharmaceutical compns. comprising, the compds. for the treatment of neurol. disorders and psychiatric disorders. Thus, (1S,2S,5R,6S)-2-[[2(S)-aminopropionyl]amino]bicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride and methanesulfonate salts were prepared via coupling reaction of N-(tert-butoxycarbonyl)-L-alanine. Compds. of the invention were active in the rat fear-potentiated startle test at 300 times lower doses when compared to (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 62 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:531823 HCAPLUS
DOCUMENT NUMBER: 137:232888
TITLE: (2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-methylcyclopropyl)Glycine Is a Potent and Selective Metabotropic Group 2 Receptor Agonist with Anxiolytic Properties
AUTHOR(S): Collado, Ivan; Pedregal, Concepcion; Mazon, Angel; Felix Espinosa, Juan; Blanco-Urgoiti, Jaime; Schoepp, Darryle D.; Wright, Rebecca A.; Johnson, Bryan G.; Kingston, Ann E.
CORPORATE SOURCE: Lilly SA, Madrid, 28108, Spain
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3619-3629
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:232888
GI



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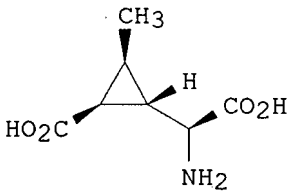


II

AB The asym. synthesis and biol. activity of (2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-methylcyclopropyl)glycine I and its epimer II (at the C3' center) are described. I is a highly potent and selective agonist for group 2 metabotropic glutamate receptors (mGluRs). It is also systemically 4 orders of magnitude more active in the fear-potentiated startle model of anxiety in rats than the rigid constrained bicyclic system LY354740. In summary, the authors have shown that high mol. complexity of conformationally constrained bicyclic systems is not a requirement to achieve highly selective and potent group 2 mGluRs agonists.

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 63 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:512129 HCAPLUS
DOCUMENT NUMBER: 137:345962
TITLE: Group II mGlu receptor agonists inhibit behavioural and electrophysiological effects of DOI in mice
AUTHOR(S): Klodzinska, Aleksandra; Bijak, Maria; Tokarski, Krzysztof; Pilc, Andrzej
CORPORATE SOURCE: Polish Academy of Sciences, Institute of Pharmacology, Krakow, 31-343, Pol.
SOURCE: Pharmacology, Biochemistry and Behavior (2002), 73(2), 327-332
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been suggested that metabotropic glutamate (mGlu) receptor agonists selective for Group II mGlu receptors may have antipsychotic action. Therefore, we studied whether the effects, which could be related to psychotomimetic action of hallucinogenic drugs, are inhibited by Group II mGlu receptor agonists. The selective mGlu2/3 agonists LY 354740 and LY 379268 inhibited (±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head twitches in mice in a dose-dependent manner. Furthermore, LY 379268 suppressed an increase in the frequency of spontaneous excitatory synaptic potentials induced by bath-applied DOI in layer V pyramidal cells recorded in the murine medial frontal cortex. The data indicate that Group II mGlu receptor agonists may counteract the effects of hallucinogenic drugs.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 64 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:512128 HCAPLUS
DOCUMENT NUMBER: 137:345961
TITLE: Modulation of DOI-induced increases in cortical BDNF

expression by group II mGlu receptors
AUTHOR(S): Gewirtz, Jonathan C.; Chen, Andrew C.; Terwilliger, Rose; Duman, Ronald C.; Marek, Gerard J.
CORPORATE SOURCE: Department of Psychiatry, Yale School of Medicine, Ribicoff Research Facilities of the Connecticut Mental Health Center, New Haven, CT, 06508, USA
SOURCE: Pharmacology, Biochemistry and Behavior (2002), 73(2), 317-326
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies have shown that 5-hydroxytryptamine2A (5-HT2A) receptor activation induces changes in the pattern of brain-derived neurotrophic factor (BDNF) mRNA expression in the neocortex and hippocampus, and that 5-HT2A receptor blockade interferes with the induction of BDNF mRNA by stress. Recent studies have also shown that activation of metabotropic glutamate group II (mGlu2/3) receptors suppresses 5-HT2A receptor-stimulated excitatory postsynaptic potentials/currents (EPSP/Cs) in pyramidal neurons in medial prefrontal cortex. Conversely, blockade of mGlu2/3 receptors enhances 5-HT-induced EPSCs. The current study examined the effects of the highly selective mGlu2/3 agonist LY 354740 and the mGlu2/3 antagonist LY 341495 on BDNF mRNA expression in medial prefrontal cortex induced by the hallucinogen and 5-HT2A/2B/2C agonist 1-(2,5-dimethoxy-4-iodophenethyl)-2-aminopropane (DOI). LY 354740 (0.1-10 mg/kg) dose-dependently suppressed DOI-induced BDNF mRNA levels in medial prefrontal cortex. In contrast, the mGlu2/3 antagonist LY 341495 (1 mg/kg) enhanced DOI-induced BDNF mRNA levels. BDNF mRNA expression was not altered by administration of the mGlu agonist or the antagonist alone. These results are discussed with respect to a potential role for group II mGlu agonists in the treatment of depression and schizophrenia.
REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 65 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:452280 HCAPLUS
DOCUMENT NUMBER: 137:163325
TITLE: Common and Selective Molecular Determinants Involved in Metabotropic Glutamate Receptor Agonist Activity
AUTHOR(S): Bertrand, Hugues-Olivier; Bessis, Anne-Sophie; Pin, Jean-Philippe; Acher, Francine C.
CORPORATE SOURCE: Accelrys, Orsay, 91893, Fr.
SOURCE: Journal of Medicinal Chemistry (2002), 45(15), 3171-3183
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several potent and group selective agonists of metabotropic glutamate receptors (mGluRs) have been docked at mGlu1,2,4R binding sites in the closed conformation of the bilobate extracellular domain. Quisqualic acid and (S)-3,5-dihydroxyphenylglycine (3,5-DHPG) were selected for mGlu1R, dicarboxycyclopropylglycine (DCG-IV), LY354740, (S)-4-carboxyphenylglycine (4CPG) for mGlu2R, and (S)-2-amino-4-phosphonobutyric acid (AP4), 1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I), (S)-4-phosphonophenylglycine (PPG) for

mGlu4R. The models show a conserved binding pattern for the glycine moiety (α-amino and α-acidic functions) and group specific bindings for the distal acidic function. The best agonists allow optimized interaction with both lobes of the binding domain. Interlobe connections around the ligand are also described and participate in stabilizing the closed form of the amino-terminal domain. Altogether, the docking models support the proposal that the stabilization of a closed state represents a key step in agonist activation of mGluRs.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 66 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:451371 HCAPLUS
DOCUMENT NUMBER: 137:164022
TITLE: Role of P/Q-Ca2+ channels in metabotropic glutamate receptor 2/3-dependent presynaptic long-term depression at nucleus accumbens synapses
AUTHOR(S): Robbe, David; Alonso, Gerard; Chaumont, Severine; Bockaert, Joel; Manzoni, Olivier J.
CORPORATE SOURCE: Centre National de la Recherche Scientifique Unite Propre de Recherche 9023, Montpellier, 34094, Fr.
SOURCE: Journal of Neuroscience (2002), 22(11), 4346-4356 CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nucleus accumbens (NAc) is an important cerebral area involved in reward and spatial memory, but little is known about synaptic plasticity in this region. Here, electron microscopy revealed that, in the NAc, metabotropic glutamate receptors 2/3 (mGlu2/3) immunostaining was essentially associated with axonal terminals and glial processes, whereas postsynaptic dendrites and neuronal cell bodies were unstained. Electrophysiol. techniques in the NAc slice preparation demonstrated that activation of mGlu2/3 with synaptically released glutamate or specific exogenous agonist, such as LY354740 (200 nM, 10 min), induced long-term depression of excitatory synaptic transmission (mGlu2/3-LTD). Tetanic-LTD and pharmacol. mGlu2/3-LTD occluded each other, suggesting common mechanisms. The mGlu2/3-LTD did not require synaptic activity but depended on the cAMP-protein kinase A cascade. Selective inhibition of P/Q-type Ca2+ channels with ω-agatoxin-IVA occluded the expression of mGlu2/3-LTD, and, conversely, the inhibitory effects of ω-agatoxin-IVA were abolished during mGlu2/3-LTD. Thus, mGlu2/3 play an important role in the control of use-dependent synaptic plasticity at prelimbic cortex-NAc synapses: their activation causes a form of LTD mediated by the long-lasting reduction of P/Q-type Ca2+ channels contribution to transmitter release.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 67 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:389494 HCAPLUS
DOCUMENT NUMBER: 137:304069
TITLE: Preclinical pharmacology of mGlu2/3 receptor agonists: novel agents for schizophrenia?
AUTHOR(S): Schoepp, Darryle D.; Marek, Gerard J.
CORPORATE SOURCE: Neuroscience Research Division, Eli Lilly and Company,

Indianapolis, IN, 46285, USA
SOURCE: Current Drug Targets: CNS & Neurological Disorders (2002), 1(2), 215-225
CODEN: CDTCCC; ISSN: 1568-007X
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Agonists for mGlu2/3 receptors decrease the evoked release of glutamate at certain (ie. forebrain / limbic) glutamatergic synapses, indicating that the functional role of mGlu2 and/or mGlu3 receptors is to suppress glutamate excitations. This offers a mechanism for dampening glutamate excitation under pathol. states resulting from excessive glutamate release. Based, in part, on the psychotomimetic actions of phencyclidine (PCP)-like drugs, excessive or pathol. glutamate release has been implicated in a number of clin. conditions including psychosis. With this in mind, the pharmacol. of multiple mGlu2/3 receptor agonists have been investigated in PCP treated rats. Agonists for mGlu2/3 receptors such as LY354740 and LY379268 have been shown to block certain behavioral responses to PCP in rats. The effects of mGlu2/3 agonists on PCP-induced behaviors are blocked by a low doses of a selective mGlu2/3 receptor antagonist, indicating that these actions are mediated via mGlu2/3 receptors. In addition, mGlu2/3 agonists potently suppress glutamate release in rat prefrontal cortex, as reflected by excitatory post-synaptic potentials (EPSPs) induced by serotonin (5-HT) acting on 5HT2A receptors. These actions of LY354740 and LY379268 are also blocked by a selective mGlu2/3 antagonist. Atypical antipsychotic drugs such as clozapine also suppress 5-HT-induced EPSPs in this brain region, thus suggesting a common pathway for the actions of atypical antipsychotic drugs and mGlu2/3 receptor agonists. As glutamatergic dysfunction has been implicated in psychotic states and possibly in the etiol. of schizophrenia, clin. studies with mGlu2/3 agonists may be warranted to further explore the validity of the glutamatergic hypothesis of schizophrenia.

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 68 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:246696 HCAPLUS
DOCUMENT NUMBER: 136:320694

TITLE: Nicotine potentiation of brain stimulation reward reversed by DHβE and SCH 23390, but not by eticlopride, LY 314582 or MPEP in rats

AUTHOR(S): Harrison, Amanda A.; Gasparini, Fabrizio; Markou, Athina
CORPORATE SOURCE: Department of Neuropharmacology, CVN-7, The Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Psychopharmacology (Berlin, Germany) (2002), 160(1), 56-66
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rationale: Systemic nicotine administration increases dopamine and glutamate levels in reward-related brain areas. Nicotine-induced increases of dopamine in the nucleus accumbens are in part mediated by glutamatergic projections to the ventral tegmental area dopamine neurons. Objectives: To assess the effects of actions at acetylcholine, dopamine, presynaptic (mGluR2/3) and postsynaptic (mGluR5) metabotropic

glutamate receptors (mGluRs) on the potentiation of brain stimulation reward induced by systemically administered nicotine (0.125-0.5 mg/kg; free base) in rats. Methods: A discrete-trial current-thresholds stimulation reward procedure (electrodes placed in the posterior lateral hypothalamus) was used to assess the effects of DHβE (0.5-5 mg/kg), an acetylcholine nicotinic receptor antagonist, SCH 23390 (1.25-5 ug/kg), a dopamine D1 receptor antagonist, eticlopride (2.5-20 μg/kg), a dopamine D2 receptor antagonist, LY 314582 (1-20 mg/kg), an mGluR2/3 agonist, and MPEP (1-9 mg/kg), an mGluR5 antagonist, on the reward potentiating effects of nicotine (0.25 mg/kg). Results: DHβE had no effect on reward thresholds when administered alone, but dose-dependently reversed the nicotine-induced potentiation of brain stimulation reward. SCH 23390 (5 μg/kg) elevated thresholds when administered alone, and reversed the nicotine-induced potentiation of brain stimulation reward even at a dose (2.5 ug/kg) that had no effect on reward thresholds. Eticlopride (10-20 μg/kg), LY 314582 (10-20 mg/kg) and MPEP (9 mg/kg) elevated thresholds when administered alone but had no effect on the nicotine-induced potentiation of brain stimulation reward. Conclusions: These results indicate that nicotinic and dopamine D1 receptors are involved in the nicotine-induced potentiation of brain stimulation reward, while actions at dopamine D2, mGlu2/3 and mGlu5 receptors did not modulate this effect of nicotine.

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 69 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:222660 HCAPLUS
DOCUMENT NUMBER: 137:241511
TITLE: Metabotropic glutamate receptors: A novel approach to treat psychiatric disorders
AUTHOR(S): Schoepp, Darryle D.; Cartmell, Jayne; Johnson, Bryan G.; Salhoff, Craig R.; Wright, Rebecca A.; Tizzano, Joseph P.; Monn, James A.
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Biomedical and Health Research (2001), 45(Excitatory Amino Acids: Ten Years Later), 207-216
CODEN: BIHREN; ISSN: 0929-6743
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The clin. investigation of glutamatergic mechanisms for psychiatric disorders has been hampered by side-effect limitations of most current agents. However, the cloning and recognition of multiple families and subtypes of glutamate receptors offers new approaches to more selectively target brain regions and specific neuronal synapses/circuits that may be relevant to the safe and effective treatment of psychiatric disorders. Metabotropic (G-protein coupled) glutamate receptors are differentially distributed in the CNS where they function to modulate excitatory and inhibitory neuronal transmission via pre- and post-synaptic mechanisms. In particular, group II mGlu receptors (mGlu2/3) are highly expressed in forebrain regions, and agonists for mGlu2/3 have been shown to suppress glutamate excitations by pre- and post-synaptic mechanisms. Suppression of glutamate excitation by novel selective mGlu2/3 receptor agonist compds. has been shown in multiple brain regions/synapses where glutamate hyper-excitation has been linked to psychiatric conditions. The

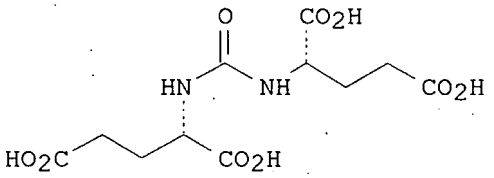
selective suppression of glutamatergic excitatory output from these brain regions may be relevant for the treatment of anxiety, psychosis, and drug withdrawal conditions. The compds. LY354740 and LY379268 are potent at nanomolar concns., highly selective and systemically active agonists for mGlu2/3 receptors. These compds. have been useful tools to explore possible therapeutic utilities of mGlu2/3 receptor agonists in animal models of psychiatric disorders, that include suppression of stress/anxiety behaviors and in the phencyclidine (PCP) model of psychosis.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 70 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:220603 HCAPLUS
DOCUMENT NUMBER: 136:263473
TITLE: Preparation of amino acid conjugates as agonists or antagonists, for a metabotropic glutamate receptor or a NAALADase enzyme for therapeutic uses
INVENTOR(S): Kozikowski, Alan P.; Wroblewski, Jarda T.; Nan, Fajun
PATENT ASSIGNEE(S): Georgetown University, USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002022627	A2	20020321	WO 2001-US28923	20010914
WO 2002022627	A3	20020704		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6528499	B1	20030304	US 2000-662767	20000915
AU 2001091001	A5	20020326	AU 2001-91001	20010914
PRIORITY APPLN. INFO.:			US 2000-662767 A	20000915
			US 2000-559978 A2	20000427
			WO 2001-US28923 W	20010914

OTHER SOURCE(S): MARPAT 136:263473
GI



I

AB Title compds. [G-W-Z(G)-Y]2X, [where X = C(O), C(S), P(O)(OR), S(O)2, C(R)(OR), or C(R)(SR); Y = (CR2)n, or bond; Z = C(R), C(NR2) or C(NH-acyl); W = (CR2)m, (NR)m, or bond; G = H, CO2H, SO3H, P(O)(OH)2, SR, or 2-R-tetrazol-5-yl; R = H, alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, or neg. charge when R is bonded to a heteroatom; m, n = independently 0 - 3; and their stereo isomers and mixts.] for use as metabotropic glutamate receptor modulators (agonists or antagonists) or NAALADase inhibitors in treating disease involving ischemia. Thus, dibenzyl L-glutamate tosylate was reacted with triphosgene to give the tetrabenzyletheruredo compound, which was deesterified to give FN11 (I). In in vivo antitumor tests using U-87 glioblastoma xenograft, I reduced tumor volume to a value of .apprx.0.4-0.6 (at 10 or 100 μM) after 4 days treatment, and .apprx. 1.0 (at both dosages) after 7 days treatment. The antiangiogenesis activity of I was examined with similarly grown tumors, and revealed a preponderance of avascular and low vascular areas in tumors treated with I at 100 μM. Studies of neuroprotective properties of FN compds. revealed that none were quite as effective as the control compound tested.

L9 ANSWER 71 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:12281 HCAPLUS
DOCUMENT NUMBER: 136:272615
TITLE: The disposition, metabolism, and pharmacokinetics of a selective metabotropic glutamate receptor agonist in rats and dogs
AUTHOR(S): Johnson, Jason T.; Mattiuz, Edward L.; Chay, Sylvia H.; Herman, Jennifer L.; Wheeler, William J.; Kassahun, Kelem; Swanson, Steven P.; Phillips, Diane L.
CORPORATE SOURCE: Lilly Research Laboratories, Department of Drug Disposition, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Drug Metabolism and Disposition (2002), 30(1), 27-33
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Compound LY354740 [(+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid], an analog of glutamic acid, is a selective group 2 metabotropic glutamate receptor agonist in clin. development for the treatment of anxiety. Studies were conducted to characterize the absorption, disposition, metabolism, and excretion of [14C]LY354740 in rats and dogs after i.v. bolus or oral administration. Plasma concns. of LY354740 were measured by gas chromatog./mass spectrometry. In rats, LY354740 demonstrated linear pharmacokinetics after oral administration of 30-1000 mg/kg. The oral bioavailability of LY354740 was approx. 10% in rats and 45% in dogs. In the dog, food decreased the mean area under the plasma concentration-time curve value by approx. 34%, hence decreasing the oral bioavailability of the compound Excretion studies in both rats and dogs indicated that the absorbed drug is eliminated primarily via renal excretion. In addition, tissue distribution in rats showed that the highest levels of radioactivity were in the kidney and gastrointestinal tract, which is consistent with the excretion studies. The metabolism of LY354740 was evaluated in vitro by using rat and dog liver microsomes and rat liver slices. In addition, urine and fecal samples from rat and dog excretion

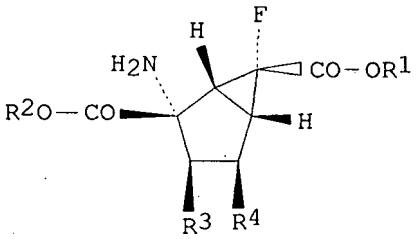
studies were profiled by using HPLC with radiodetection. These evaluations indicated that neither rats nor dogs metabolized LY354740. Thus, LY354740 is poorly absorbed in rats, moderately absorbed in dogs, and rapidly excreted as unchanged drug in the urine.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 72 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:10425 HCAPLUS
DOCUMENT NUMBER: 136:85627
TITLE: Preparation of bicyclo[3.1.0]dicarboxylic acid derivatives as group 2 metabotropic glutamate receptor agonists
INVENTOR(S): Nakazato, Atsuro; Kumagai, Toshihito; Kanuma, Kosuke; Sakagami, Kazunari
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000605	A1	20020103	WO 2001-JP5550	20010628
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001067854	A5	20020108	AU 2001-67854	20010628
CA 2411059	A1	20021206	CA 2001-2411059	20010628
EP 1295865	A1	20030326	EP 2001-945657	20010628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003134902	A1	20030717	US 2002-297479	20021206
US 6770676	B2	20040803		
HK 1056868	A1	20051202	HK 2003-109245	20031219
PRIORITY APPLN. INFO.:			JP 2000-195239 A	20000628
			WO 2001-JP5550 W	20010628

OTHER SOURCE(S): MARPAT 136:85627
GI



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AB 2-Amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs. represented by the general formula I [R1, R2 = H, alkyl, etc.; when R3 is OH, R4 is H; or R3R4 = bond] are prepared These compds. are useful as drugs, in particular, group 2 metabotropic glutamate receptor agonists having therapeutic and preventive effects on, for example, psychiatric diseases such as schizophrenia, anxiety, etc. (1R,2R,3R,5R,6R)-2-Amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid was prepared and its bioactivity was demonstrated.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 73 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:925011 HCAPLUS
DOCUMENT NUMBER: 136:318765
TITLE: Pharmacophore identification and bioactivity prediction for group I metabotropic glutamate receptor agonists by the electron-conformational QSAR method
AUTHOR(S): Rosines, Eran; Bersuker, Isaac B.; Boggs, James E.
CORPORATE SOURCE: Institute for Theoretical Chemistry, Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX, 78712, USA
SOURCE: Quantitative Structure-Activity Relationships (2001), 20(4), 327-334
CODEN: QSARDI; ISSN: 0931-8771
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacophore for group I metabotropic glutamate receptor (mGluR1) agonists is revealed and their activity predicted by means of the previously developed and further improved electron-conformational (EC) method. A distinguishing feature of this method is that in addition to revealing the pharmacophore of activity as a set of specific atomic electronic features arranged in a special geometry, it allows for prediction of the activity quant. as a function of the parameters of pharmacophore flexibility and anti-pharmacophore shielding groups. Conformational anal., electronic structure calcns., and matrix processing are performed for the training set of 29 compds., 13 active and 16 inactive, and the pharmacophore of mGluR1 agonists is evaluated. It contains a four-point skeleton of three oxygen atoms and one nitrogen atom at certain interat. distances with restricted atomic interaction indexes whereby all these parameters are determined within certain tolerances. The pharmacophore parameter flexibilities, as well as the influence of the anti-pharmacophore shielding and other auxiliary groups are parameterized and weighted by seven consts., their values being obtained from a least-square regression with very good statistics: R2 = 0.97, F = 589 (.apprx.100% level of confidence), and a standard error of about 5% of the range of measured values. The results are also tested with the leave-one-out cross validation method that yields prediction statistics R2 = 0.91. The E statistics were also evaluated illustrating the role of each of the activity parameters involved.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 74 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:900257 HCAPLUS

DOCUMENT NUMBER: 136:279664
TITLE: Stereoselective synthesis of 2-amino-3-fluoro bicyclo[3.1.0]hexane-2,6-dicarboxylic acid
AUTHOR(S): Pedregal, Concepcion; Prowse, William
CORPORATE SOURCE: Centro de Investigacion Lilly, Madrid, 28108, Spain
SOURCE: Bioorganic & Medicinal Chemistry (2001), Volume Date 2002, 10(2), 433-436
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:279664
AB (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) is a conformationally restricted glutamate analog that is a potent, selective and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. Herein, we describe a stereoselective and highly efficient synthesis of its 3-beta fluoro derivative using the Corey-Link methodol. to create the amino acid stereogenic center.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 75 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:899180 HCAPLUS
DOCUMENT NUMBER: 136:242020
TITLE: Group 2 metabotropic glutamate receptors induced long term depression in mouse striatal slices
AUTHOR(S): Kahn, Laetitia; Alonso, Gerard; Robbe, David; Bockaert, Joel; Manzoni, Olivier J.
CORPORATE SOURCE: CNRS UPR 9023, Montpellier, 34094, Fr.
SOURCE: Neuroscience Letters (2001), 316(3), 178-182
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied the roles of mGlu2/3 receptors (mGlu2/3) in glutamatergic transmission at corticostriatal synapses in mice brain slices. Perfusion of the selective mGlu2/3 agonists LY 354740 and L-CCG1 caused the long term depression (LTD) of evoked synaptic responses. Photonic and electronic microscopy showed mGlu2/3 on axonal fibers and glial processes but not on striatal dendrites. The mGlu2/3-LTD was independent of synaptic activity and insensitive to specific antagonists of dopamine D1, D2, GABAB, NMDA, or adenosine A1 receptors. Manipulation of the cAMP/protein kinase A cascade had no effect on the mGlu2/3-LTD. In contrast, MEK1-2 inhibitors reduced both mGlu2/3 initial depression and LTD suggesting the involvement of the MAP kinase pathway in mGlu2/3-LTD.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 76 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:884587 HCAPLUS
DOCUMENT NUMBER: 136:177852
TITLE: The antianxiety-like effects of antagonists of group I and agonists of group II and III metabotropic glutamate receptors after intrahippocampal administration

AUTHOR(S): Tatarczynska, Ewa; Klodzinska, Aleksandra; Kroczka, Bernadetta; Chojnacka-Wojcik, Ewa; Pilc, Andrzej
CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences, Smetna, 12, Pol.
SOURCE: Psychopharmacology (Berlin, Germany) (2001), 158(1), 94-99
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rationale: Substances acting as agonists of group II mGlu receptors with joint group I mGlu receptor antagonist effects, or group II mGlu receptors agonists, were shown to induce antianxiety-like effect in rats after intrahippocampal administration. Objective: The present study was undertaken to establish whether a more selective group I, II, III mGlu receptors agonists/antagonists induce anxiolytic-like effects after injection to the hippocampus. Methods: (S)-4-Carboxyphenylglycine [(S)-4CPG] and 7-(hydroxyimino)cyclopropan[b]chromen-1α-carboxylic Et ester (CPCCOEt), selective antagonists at group I mGlu receptors, or (+)1S, 2S, 5R, 6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) and (2S, 1'S, 2'S)-2-(carboxycyclopropyl)glycine (L-CCG-I), two selective agonists of group II mGlu receptors, as well as (1S, 2S, 4S, 5S)-2-aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid-I (ABHxD-I), an agonist at all three groups of mGlu receptors and L-serine-O-phosphate (L-SOP), an agonist at group III mGlu receptors, were used. All compds. were administered into the CA1 region of the dorsal hippocampus. The conflict drinking Vogel test in rats was used to estimate the anxiolytic-like effects of all the compds. Results: After intrahippocampal administration, both selective group I mGlu receptors antagonists (S)-4CPG and CPCCOEt, as well as the selective agonists of group II mGlu receptors LY 354740 and L-CCG-I, and an agonist of group III mGlu receptors, L-SOP, induced anticonflict effects. Conclusion: Selective antagonists of group I mGlu receptors and agonists of group II and group III mGlu receptors exhibit anxiolytic-like activity in the conflict drinking test. It seems that the hippocampus may be one of the brain structures involved in the anticonflict effect of mGlu receptor agonists/antagonists.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 77 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:783709 HCAPLUS
DOCUMENT NUMBER: 136:115819
TITLE: Identification of essential residues involved in the glutamate binding pocket of the group II metabotropic glutamate receptor
AUTHOR(S): Malherbe, Pari; Knoflach, Frederic; Broger, Clemens; Ohresser, Serge; Kratzeisen, Claudia; Adam, Geo; Stadler, Heinz; Kemp, John A.; Mutel, Vincent
CORPORATE SOURCE: Pharma Division, Preclinical Research, Nervous System Diseases, F. Hoffmann-La Roche Ltd., Basel, Switz.
SOURCE: Molecular Pharmacology (2001), 60(5), 944-954
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Metabotropic glutamate (mGlu) receptors are a family of G-protein-coupled receptors that play central roles as modulators of both glutamatergic and other major neurotransmitter systems in CNS. Using mol. modeling, site-directed mutagenesis, [3H]LY354740 binding, [35S]GTPγS binding, and activation of GIRK current, we have been able to identify residues crucial for the binding of LY354740 and glutamate to rat mGlu2 receptors. Several of the crucial residues located in the binding site (Arg-57, Tyr-144, Tyr-216, Asp-295) have not been identified previously. We propose that the γ-carboxyl group of LY354740 forms H-bonds to Arg-57, whereas the α-carboxyl group forms an H-bond with the hydroxyl group of Ser-145. The α-amino group of LY354740 forms H-bonds to Asp-295 and to the side-chain hydroxyl group of Thr-168. In addition, Tyr-144 may establish a hydrophobic (C-H/π)-interaction with the bicyclo-hexane ring of LY354740. Furthermore, the mutation of residues Ser-148 and Arg-183, which are too remote for a direct interaction, affected the ligand affinity dramatically. These results suggest that Ser-148 and Arg-183 may be important for the 3D structure and/or are involved in closure of the domain. Finally, Asp-146, which is also remote from the binding site, was shown to be involved in the differential binding affinity of [3H]LY354740 for mGlu2 vs. mGlu3 receptors. All the mGlu receptors except mGlu2 are activated by Ca2+ and have serine instead of aspartic acid at this position, which suggests a critical role of this aspartic acid residue in the binding properties of this unique receptor.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 78 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:626789 HCAPLUS
DOCUMENT NUMBER: 136:15136
TITLE: LY354740 attenuates the expression of long-term behavioral sensitization induced by a single session of foot shocks
AUTHOR(S): Bruijnzeel, A. W.; Stam, R.; Wiegant, V. M.
CORPORATE SOURCE: Division of Pharmacology and Anatomy, University Medical Center Utrecht, Rudolf Magnus Institute for Neurosciences, Utrecht, 3508 AB, Neth.
SOURCE: European Journal of Pharmacology (2001), 426(1,2), 77-80
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exposure of rats to a single session of foot shocks sensitizes behavioral responses to novel stimuli. There is evidence that metabotropic glutamate (mGlu) receptors play a role in sensitization processes. In the present study, the authors investigated the role of mGlu2/3 receptors in the long-term (14 days) increase in defensive withdrawal behavior after a single session of foot shocks. Exposure to foot shocks increased defensive withdrawal behavior. The mGlu2/3 receptor agonist LY354740 ((1S,2S,5R,6S)-(+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 0.1 mg/kg, i.p.) normalized the increased latency and the decreased time in the light of the preshocked rats. The authors conclude that activation of mGlu2/3 receptors attenuates the foot shock-induced expression of behavioral sensitization.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 79 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:573843 HCAPLUS
DOCUMENT NUMBER: 135:327653
TITLE: Activation of group II metabotropic glutamate receptors results in long-term potentiation following preconditioning stimulation in the dentate gyrus
AUTHOR(S): Rush, A. M.; Wu, J.; Rowan, M. J.; Anwyl, R.
CORPORATE SOURCE: Department of Physiology, Trinity College Dublin, Dublin, Ire.
SOURCE: Neuroscience (Oxford, United Kingdom) (2001), 105(2), 335-341
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of group II metabotropic glutamate receptors in the induction/expression of long-term potentiation has been investigated in the medial perforant path of the outer (infrapyramidal) blade of the rat dentate gyrus in vitro. Activation of group II metabotropic glutamate receptors by perfusion of the selective agonist LY354740 did not induce long-term potentiation or long-term depression in control. However, LY354740, applied following the induction of long-term potentiation by high frequency stimulation, resulted in addnl. long-term potentiation. LY354740 was only found to cause addnl. long-term potentiation if the pre-existing high frequency stimulation-induced long-term potentiation was sub-maximal. Although activation of metabotropic glutamate receptors was not required for induction of high frequency stimulation-induced long-term potentiation, activation of both group I and group II metabotropic glutamate receptors was required during high frequency stimulation-induced long-term potentiation in order for subsequent application of LY354740 to result in addnl. long-term potentiation. Thus, the long-term potentiation caused by application of LY354740 following high frequency-induced long-term potentiation was prevented if the high frequency stimulation was given in the presence of (S)-α-methyl-4-carboxyphenylglycine or the selective group I or group II metabotropic glutamate receptor antagonists 1-aminoindan-1,5-dicarboxylic acid or (2S)-α-ethylglutamic acid resp. The long-term potentiation caused by LY354740 was also dependent upon activation of N-methyl-D-aspartate receptors during the high frequency stimulation, being blocked if high frequency stimulation was given in the presence of the N-methyl-D-aspartate receptor antagonist, D(-)-2-amino-5-phosphonopentanoic acid. The long-term potentiation resulting from activation of group II metabotropic glutamate receptors could be due either to the enhancement of the expression level of the high frequency stimulation-induced long-term potentiation, or alternatively, to a direct novel induction of long-term potentiation. In either theory, the long-term potentiation resulting from activation of group II metabotropic glutamate receptors is dependent upon prestimulation of group I and group II metabotropic glutamate receptors and N-methyl-D-aspartate receptors during the 'preconditioning high frequency stimulation'.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 80 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:550150 HCAPLUS
DOCUMENT NUMBER: 136:273050
TITLE: Interactions between LY354740, a group II metabotropic agonist and the GABAA-benzodiazepine receptor complex in the rat elevated plus-maze
AUTHOR(S): Ferris, P.; Seward, E.; Dawson, G. R.
CORPORATE SOURCE: Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, UK
SOURCE: Journal of Psychopharmacology (London, United Kingdom) (2001), 15(2), 76-82
CODEN: JOPSEQ; ISSN: 0269-8811
PUBLISHER: SAGE Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Flumazenil, a benzodiazepine (BZ) receptor antagonist, and naloxone, a non-selective μ-receptor antagonist, were used to investigate whether the anxiolytic action of LY354740 [1S,2S,5R,6S-2-amino bicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate], a Group II metabotropic glutamate receptor agonist, was mediated through the benzodiazepine binding site on the GABAA receptor and opioid pathways. LY354740 (1.0-10.0 mg/kg i.p.) induced dose-dependent anxiolytic-like effects in the rat elevated plus-maze. The anxiolytic-like effects of LY354740 (10.0 mg/kg) and the benzodiazepine receptor agonist, chlordiazepoxide (CDP, 5.0 mg/kg i.p.) were blocked by flumazenil (15.0 mg/kg i.p.). By contrast, naloxone (10.0 mg/kg i.p.) failed to affect the anxiolytic-like effects of either LY354740 or CDP. The behavior of animals treated with flumazenil or naloxone alone did not significantly differ from that of animals treated with vehicle alone. This study suggests that the anxiolytic-like effects of LY354740 on the elevated plus-maze may be directly or indirectly mediated by the benzodiazepine binding site on the GABAA receptor complex.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 81 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:546912 HCAPLUS
DOCUMENT NUMBER: 135:236900
TITLE: [3H]LY341495 binding to group II metabotropic glutamate receptors in rat brain
AUTHOR(S): Wright, Rebecca A.; Arnold, M. Brian; Wheeler, William J.; Ornstein, Paul L.; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 298(2), 453-460
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB [3H]LY 341495 is a highly potent and selective antagonist for group II metabotropic glutamate (mGlu) receptors (mGlu2 and mGlu3), which has been used to label these receptors in cells expressing recombinant receptor subtypes. In this study, we characterized the kinetics, pharmacol., and distribution of [3H]LY 341495 binding to mGlu receptors in rat brain tissue. Equilibrium expts. in the rat forebrain demonstrated binding to a

single site that was saturable, reversible, and of high affinity (Bmax, 3.9 pmol/mg of protein, Kd, 0.84 nM). The relative order of potencies for displacement of [3H]LY 341495 by mGlu receptor ligands was LY 341495 >> L-glutamic acid > LY 354740 > (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine > 4-(2R,4R)-aminopyrrolidine-2,4-dicarboxylate > (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid > (R,S)-α-methyl-4-phosphonophenylglycine > (R,S)3,5-dihydroxyphenylglycine > L-(+)-2-amino-4-phosphonobutyric acid. [3H]LY 341495 was not displaced by the selective ionotropic glutamate receptor agonists N-methyl-D-aspartic acid, (R,S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or kainate at concns. up to 1 mM. Comparison of [3H]LY 341495 binding in rat brain with recombinant mGlu receptor subtypes demonstrated a very high correlation with mGlu3 receptor binding (r2 = 0.957), a significant, but lower, correlation with mGlu2 receptor binding (r2 = 0.869), but no significant correlation to mGlu8 receptor binding (r2 = 0.284). Regional studies using autoradiog. showed a similar distribution of [3H]LY 341495 binding to that for group II mGlu receptors previously reported by others using immunocytochem. techniques. These studies indicate that [3H]LY 341495 selectively labels group II (mGlu2/3) receptors, but under the conditions used, [3H]LY 341495 may bind predominately to mGlu3 receptor populations in the rat forebrain.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 82 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:533059 HCAPLUS

DOCUMENT NUMBER: 135:221672

TITLE: Group II and III metabotropic glutamate receptors contribute to different aspects of visual response processing in the rat superior colliculus

AUTHOR(S): Cirone, Jennifer; Salt, Thomas E.

CORPORATE SOURCE: Department of Visual Science, Institute of Ophthalmology, University College London, London, EC1V 9EL, UK

SOURCE: Journal of Physiology (Cambridge, United Kingdom) (2001), 534(1), 169-178
CODEN: JPHYA7; ISSN: 0022-3751

PUBLISHER: Cambridge University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Neurons in the superior colliculus (SC) respond to novel sensory stimuli and response habituation is a key feature of this. It is known that both ionotropic and metabotropic glutamate (mGlu) receptors participate in visual responses of superficial SC neurons. A feature of Group II and Group III mGlu receptors is that they may modulate specific neural pathways, possibly via presynaptic mechanisms. However, less is known about how this may relate to functions of systems in whole animals. We have therefore investigated whether these receptors affect specific attributes of visual responses in the superficial SC. Recordings were made from visually responsive neurons in anesthetized rats, and agonists and antagonists of Group II and III mGlu receptors were applied iontophoretically at the recording site. We found that application of the Group III metabotropic glutamate receptor agonist L-2-amino-4-phosphonobutyric acid (L-AP4) produced an increase in visual response habituation, while Group III antagonists decreased habituation. These effects were independent of the response habituation mediated via GABAB receptors. In contrast, modulation of Group II mGlu

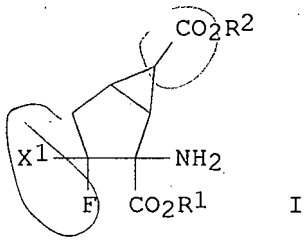
receptors with the specific agonist LY 354740 or the antagonist LY 341495 did not affect response habituation, although these compds. did modulate visual responses. This suggests a specific role for Group III mGlu receptors in visual response habituation. The magnitude of Group II effects was smaller during presentation of low contrast stimuli compared with high contrast stimuli. This suggests that activation of Group II receptors may be activity dependent and that these receptors can translate this into a functional effect in adapting to high contrast stimuli.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 83 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:237831 HCAPLUS
DOCUMENT NUMBER: 134:261265
TITLE: Fluorinated amino acid derivatives for treatment of mental disorders
INVENTOR(S): Nakazato, Atsuo; Kumagaya, Toshihito; Sakagami, Kazunari; Tomizawa, Kazuyuki
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001089367	A	20010403	JP 2000-215701	20000717
PRIORITY APPLN. INFO.:			JP 1999-206309 A	19990721

OTHER SOURCE(S): MARPAT 134:261265
GI



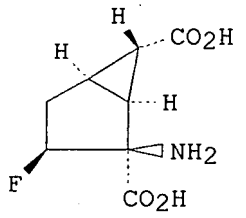
I

AB Fluorinated amino acid derivs. (I; X1 = H, F;R1, R2 = H, C1-10 alkyl), including (1S,2S,3S,5R,6S)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, and their pharmaceutically acceptable salts are claimed as group-2 metabotropic glutamate receptor agonists for treatment of mental disorders, e.g. schizophrenia, anxiety, depression, bipolar disorder, drug dependence, cognition disorder, Alzheimer disease, Huntington's disease, brain ischemia, Parkinsonism, spinal injury, etc. I were prepared, and their antipsychotic effects were tested in animal models.

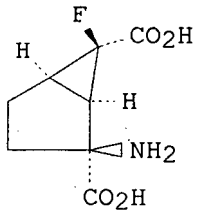
L9 ANSWER 84 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:874698 HCAPLUS
DOCUMENT NUMBER: 134:142137
TITLE: Pharmacological properties of native metabotropic glutamate receptors in freshly dissociated Golgi cells of the rat cerebellum
AUTHOR(S): Knoflach, F.; Woltering, T.; Adam, G.; Mutel, V.; Kemp, J. A.
CORPORATE SOURCE: Pharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, 4070, Switz.
SOURCE: Neuropharmacology (2001), 40(2), 163-169
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have examined the pharmacol. properties of native metabotropic glutamate (mGlu) receptors in freshly isolated rat cerebellar Golgi cells using the whole-cell configuration of the patch-clamp technique. Group II mGlu receptor agonists inhibited voltage-gated Ca2+ channels (VGCC) currents in a reversible and concentration-dependent manner with a rank order of potency being LY 354740> DCG-IV > L-CCG-I > glutamate >> 1S,3R-ACPD > NAAG. The maximum degree of inhibition obtained was similar for all drugs tested, saturating at about 33-41%, except for NAAG that had a non saturating effect of 50% at 1 mM. Two novel group II mGlu receptor antagonists, LY 341495 and Ro 65-3479, reversed VGCC current inhibition by LY 354740 with pKB values of 7.0 and 6.3, resp. In a subpopulation of Golgi cells, the antagonistic effect of LY 341495 was only partial, suggesting a remaining effect of group I mGlu receptors. This was confirmed by expts. with S-DHPG, a selective group I mGlu receptor agonist. These expts. suggest that Golgi cells of the cerebellum express group II mGlu receptors that couple to the inhibition of VGCCs. Therefore, inhibition of VGCCs in cerebellar Golgi cells is a useful model system to evaluate novel group II mGlu receptor ligands.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 85 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:818585 HCAPLUS
DOCUMENT NUMBER: 134:131259
TITLE: Synthesis, SARs, and Pharmacological Characterization of 2-Amino-3- or -6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid Derivatives as Potent, Selective, and Orally Active Group II Metabotropic Glutamate Receptor Agonists
AUTHOR(S): Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Yoshikawa, Ryoko; Suzuki, Yoshiko; Chaki, Shigeyuki; Ito, Hisanaka; Taguchi, Takeo; Nakanishi, Shigetada; Okuyama, Shigeru
CORPORATE SOURCE: 1st Laboratory Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ohmiya, Saitama, 330-8530, Japan
SOURCE: Journal of Medicinal Chemistry (2000), 43(25), 4893-4909
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

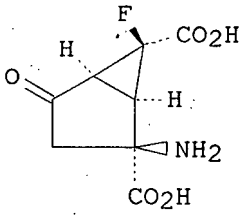
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:131259
GI



I



II



III

AB (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY 354740), a highly selective and orally active group II metabotropic glutamate receptor (mGluR) agonist, has increased interest in the study of group II mGluRs. Interest focused on a conformationally constrained form of LY 354740 because it appeared that the rigid form resulted in not only selectivity for group II mGluR but was orally active. Therefore, a fluorine atom was introduced to LY 354740 based on the mol. size (close resemblance to hydrogen atom) and electronegativity (effects on the electron distribution in the mol.) of this atom and carbon-fluorine bond energy. (+)-I (MGS 0008), the best compound among 3-fluoro derivs., retained the agonist activity of LY 354740 for mGluR2 and mGluR3 and increased the oral activity of LY 354740 for phencyclidine (PCP)-induced hyperactivity and PCP-induced head-weaving behavior. Due to the successful results of I, efforts were focused on the introduction of a fluorine atom on the C6 position of LY 354740. (-)-II exhibited a high degree of agonist activity for group II mGluRs equal to that of LY 354740 or (+)-I. Interest shifted to modification on CH2 at the C4 position of compound II, since replacement of the CH2 group with either an oxygen or sulfur atom yielded increased agonist activity. A carbonyl group instead of CH2 was positioned at C4 of II because it might slightly change the relative conformation of three functional groups, the amino group and two carboxylic acids, which have important roles in mediating the interaction between group II mGluRs and their ligand, compared with the CH2 group or the oxygen or sulfur atoms of other compds. (+)-III (MGS 0028) exhibited a remarkably high degree of agonist activity for mGluR2 expressed in CHO cells but not mGluR4, and it strongly inhibited phencyclidine (PCP)-induced head-weaving behavior and hyperactivity in rats. Thus, (+)-I and (+)-III are potent, selective, and orally active group II mGluR agonists and might be useful not only for exploring the functions of mGluRs but in the treatment of schizophrenia.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 86 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:740395 HCAPLUS
DOCUMENT NUMBER: 134:25302
TITLE: The role of metabotropic glutamate receptor (mGluR) ligands in parkinsonian muscle rigidity
AUTHOR(S): Wolfarth, S.; Konieczny, J.; Lorenc-Koci, E.; Ossowska, K.; Pilc, A.

CORPORATE SOURCE: Department of Neuropsychopharmacology, Institute of Pharmacology, Polish Academy of Sciences, Krakow, Pol.
SOURCE: Amino Acids (2000), 19(1), 95-101
CODEN: AACIE6; ISSN: 0939-4451
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been shown that the primary striatal dopaminergic hypofunction which is at the origin of Parkinson's disease, results in a secondary hyperactivity of glutamatergic neurotransmission. In the search for a therapy of Parkinson's disease, ionotropic, mainly NMDA, receptor antagonists were found to have moderately beneficial, yet also some undesirable side-effects. Therefore the present study was aimed at determining whether some metabotropic glutamate receptor (mGluR) ligands may have antiparkinsonian effects in the haloperidol-induced muscle rigidity. To this end three mGluR ligands were used: the potent and selective mGluR I antagonist (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA), the mixed group II agonist/group I antagonist (S)-4-carboxy-3-hydroxyphenyl-glycine ((S)-4-C3HPG), and the potent group II agonist (+)-2-aminobicyclo[3.1.0.]hexane-2,6,-dicarboxylic acid (LY354740). Only LY354740 penetrated the brain from the periphery; for this reason other drugs were injected bilaterally into the rostral striatum or nucleus accumbens. The muscle tone was recorded by a mechanomyog./electromyog. (MMG/EMG) method which measured the resistance of a rat's hind foot and the EMG reflex response of its muscles to passive movements. (S)-4C3HPG (5 and 15μg/0.5μl) and LY354740 (5 and 10 mg/kg i.p.) diminished the muscle rigidity induced by haloperidol (1 mg/kg i.p.). AIDA (0.5-15μg/0.5μl) injected into the striatum was only slightly effective in the highest dose used. However, when injected into the nucleus accumbens AIDA (15μg/0.5μl) significantly and strongly counteracted the haloperidol-induced muscle rigidity. Our results suggest that stimulation of group II striatal mGluRs seems to play a major role in diminution of parkinsonian-like muscle rigidity. However, it seems that the antagonism of group I mGluRs located in the nucleus accumbens may also be of importance to the antiparkinsonian effect.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 87 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:719198 HCAPLUS
DOCUMENT NUMBER: 134:290247
TITLE: Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors
AUTHOR(S): Gewirtz, J. C.; Marek, G. J.
CORPORATE SOURCE: Department of Psychiatry, Connecticut Mental Health Center, Yale School of Medicine, The Ribicoff Research Facilities, New Haven, CT, 06508, USA
SOURCE: Neuropsychopharmacology (2000), 23(5), 569-576
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent electrophysiol. studies have demonstrated a physiol. interaction between 5-HT2A and metabotropic glutamate2/3 (mGlu2/3) receptors in the medial prefrontal cortex. Several behavioral studies have found that phenethylamine hallucinogens with partial agonist activity at 5-HT2A

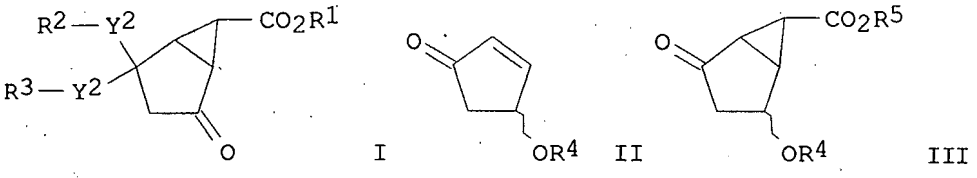
receptors induce head shakes when directly administered into the medial prefrontal cortex. The present expts. examined whether an interaction occurs between mGlu2/3 and 5-HT2A receptors on a behavioral level by studying head shakes induced in rats by phenethylamine hallucinogens as a model of 5-HT2A receptor activation. Administration of the mGlu2/3 agonist LY354740 (0.3-10 mg/kg, i.p.) suppressed head shakes induced by the phenethylamine hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). Conversely, administration of the mGlu2/3 antagonist LY341495 (1 mg/kg, i.p.) enhanced the frequency of DOI-induced head shakes. These results raise the possibility that the psychotomimetic properties of hallucinogenic drugs may be mediated in part via increased glutamate release following activation of 5-HT2A receptors.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 88 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:707118 HCAPLUS
DOCUMENT NUMBER: 133:252073
TITLE: Novel 2-oxobicyclo[3.1.0]hexane-6-carboxylic acid derivatives and process for producing the same
INVENTOR(S): Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Tomisawa, Kazuyuki
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000058258	A1	20001005	WO 2000-JP969	20000221
W: AU, CA, CN, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2368454	A1	20001005	CA 2000-2368454	20000221
EP 1164121	A1	20011219	EP 2000-904066	20000221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 754318	B2	20021114	AU 2000-25753	20000221
AU 2000025753	A	20001016		
CN 1134399	B	20040114	CN 2000-808034	20000221
JP 2000336068	A	20001205	JP 2000-44940	20000222
US 6479674	B1	20021112	US 2001-937212	20010924
US 2002156299	A1	20021024	US 2002-176528	20020624
US 6500958	B2	20021231		
HK 1047081	A1	20041203	HK 2002-108503	20021125

PRIORITY APPLN. INFO.: JP 1999-82608 A 19990325
WO 2000-JP969 W 20000221
US 2001-937212 A3 20010924
OTHER SOURCE(S): CASREACT 133:252073; MARPAT 133:252073
GI



AB The title compds. [I; wherein R1 represents hydrogen, C1-6 alkyl, C3-6 cycloalkyl, C1-6 alkyl substituted by C3-6 cycloalkyl, aryl, C1-6 alkyl substituted by aryl, C1-6 alkyl substituted by C1-6 alkoxy, C1-6 hydroxyalkyl, C1-6 alkyl substituted by C1-6 alkylthio, C1-6 mercaptoalkyl, tetrahydrofuranyl, or tetrahydropyranyl; R2 and R3 are the same or different and each represents C1-6 alkyl, C3-6 cycloalkyl, C1-6 alkyl substituted by C3-6 cycloalkyl, aryl, or C1-6 alkyl substituted by aryl, or R2 and R3 in combination represent (CH2)n (n is 2 or 3); and Y1 and Y2 are the same or different and each represents sulfur, oxygen, or nitrogen] are prepared via cycloaddn. reaction of 2-cyclopenten-4-on-1-ol derivs. (II; R4 represents H or HO-protecting group) with sulfonium ylide formula Me2S:CHCO2R5 (R5 represents groups described in R4) or sulfonium salt of formula Me2S+CH2CO2R5.X- (R5 is same as above; X represents Cl, Br, or iodo) to give 2-hydroxybicyclo[3.1.0]hexane-6-carboxylic acid derivs. (III; R4 and R5 are same as above). These compds. I are useful as intermediates in the efficient synthesis of 2-amino-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs. which act on group 2 metabotropic glutamate receptor and are useful for the treatment of psychiatric diseases such as schizophrenia, anxiety, depression, and epilepsy and nerve diseases such as Alzheimer's and Parkinson's disease. Thus, a toluene solution of 18 g 4-tert-butyldimethylsilyloxy-2-cyclopentenone (60 mL) was added under ice-cooling to a toluene solution of 13.6 g Et (dimethylsulfanylidene)acetate (120 mL), stirred at room temperature for 6 h, followed by adding another portion of a toluene solution of 24.0 g Et (dimethylsulfanylidene)acetate (120 mL) at 0°, and the resulting mixture was stirred at room temperature overnight to give a mixture of (1SR,4RS,5RS,6SR)- and (1SR,4SR,5RS,6SR)-Et 4-tert-butyldimethylsilyloxy-2-oxobicyclo[3.1.0]hexane-6-carboxylate (19.0 g). Et2O.BF3 (2.1 mL) was added to a solution of the latter mixture (16.8 g) and 5.7 mL ethanedithiol and stirred at room temperature for 2 days to give a mixture of (1SR,4RS,5RS,6SR)- and (1SR,4SR,5RS,6SR)-Et 2,2-ethylenedithio-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate (13.7 g). To a DMSO solution of the latter mixture (13.1 g) (520 mL) were successively added 40.5 g DCC, 5.0 mL pyridine, and 2.8 mL CF3CO2H at 15°, and the resulting mixture was stirred 1 day to give a mixture of (1RS,5RS,6RS)-Et 4,4-ethylenedithio-2-oxobicyclo[3.1.0]hexane-6-carboxylate (10.5 g). A mixture of the latter compound 73.2, ammonium carbonate 68.1, and KCN 20.8 g in 460 mL ethanol and 307 mL H2O was stirred at 35° for 2 days and at 0° for 2 h to give 35.2 g (1RS,2SR,5RS,6RS)-Et 2-spiro-5'-hydantoin-4,4-ethylenedithiobicyclo[3.1.0]hexane-6-carboxylate.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 89 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:633789 HCAPLUS
DOCUMENT NUMBER: 134:95381
TITLE: Cocaine and kindling alter the sensitivity of group II and III metabotropic glutamate

receptors in the central amygdala
AUTHOR(S): Neugebauer, Volker; Zinebi, Fatiha; Russell, Rex; Gallagher, Joel P.; Shinnick-Gallagher, Patricia
CORPORATE SOURCE: Department of Pharmacology and Toxicology, The University of Texas Medical Branch, Galveston, TX, 77555-1031, USA
SOURCE: Journal of Neurophysiology (2000), 84(2), 759-770
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB G-protein-coupled metabotropic glutamate receptors (mGluRs) are being implicated in various forms of neuroplasticity and CNS disorders. This study examined whether the sensitivities of mGluR agonists are modulated in a distinct fashion in different models of synaptic plasticity, specifically, kindling and chronic cocaine treatment. The influence of kindling and chronic cocaine exposure in vivo was examined in vitro on the modulation of synaptic transmission by group II and III metabotropic glutamate receptors using whole cell voltage-clamp recordings of central amygdala (CeA) neurons. Synaptic transmission was evoked by elec. stimulation of the basolateral amygdala (BLA) and ventral amygdaloid pathway (VAP) afferents in brain slices from control rats and from rats treated with cocaine or exposed to three to five stage-five kindled seizures. This study shows that after chemical stimulation with chronic cocaine exposure or after elec. stimulation with kindling the receptor sensitivities for mGluR agonists are altered in opposite ways. In slices from control rats, group II agonists, (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine (LCCG1) and (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), depressed neurotransmission more potently at the BLA-CeA than at the VAP-CeA synapse while group III agonist, L(+)-2-amino-4-phosphonobutyrate (LAP4), depressed neurotransmission more potently at the VAP-CeA synapse than at the BLA-CeA. These agonist actions were not seen (were absent) in amygdala neurons from chronic cocaine-treated animals. In contrast, after kindling, concentration response relationships for LCCG1 and LAP4 were shifted to the left, suggesting that sensitivity to these agonists is increased. Except at high concns., LCCG1, LY354740, and LAP4 neither induced membrane currents nor changed current-voltage relationships. Loss of mGluR inhibition with chronic cocaine treatment may contribute to counter-adaptive changes including anxiety and depression in cocaine withdrawal. Drugs that restore the inhibitory effects of group II and III mGluRs may be novel tools in the treatment of cocaine dependence. The enhanced sensitivity to group II and III mGluR agonists in kindling is similar to that recorded at the lateral to BLA synapse in the amygdala where they reduce epileptiform bursting. These findings suggest that drugs modifying mGluRs may prove useful in the treatment of cocaine withdrawal or epilepsy.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 90 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:460466 HCAPLUS
DOCUMENT NUMBER: 133:203281
TITLE: Group II selective metabotropic glutamate receptor agonists and

local cerebral glucose use in the rat
AUTHOR(S): Lam, Amy G. M.; Monn, James A.; Schoepp, Darryle D.; Lodge, David; McCulloch, James
CORPORATE SOURCE: Wellcome Surgical Institute and Hugh Fraser Neuroscience Laboratories, University of Glasgow, Glasgow, G61 1QH, UK
SOURCE: Journal of Cerebral Blood Flow and Metabolism (1999), 19(10), 1083-1091
CODEN: JCBMDN; ISSN: 0271-678X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel mGluR agonist LY354740 and a related analog LY379268 are selective for mGluR2/3 receptors and are centrally active after systemic administration. In this study, rates of local cerebral glucose use were measured using the [14C]2-deoxyglucose autoradiog. technique to examine the functional consequences of their systemic administration in the conscious rat. Both LY354740 (0.3, 3.0, 30 mg/kg) and LY379268 (0.1, 1.0, 10 mg/kg) produced dose-dependent changes in glucose use. After LY354740 (3.0 mg/kg), 4 of the 42 regions measured showed statistically significant changes from vehicle-treated controls: red nuclei (-16%), mammillary body (-25%), anterior thalamus (-29%), and the superficial layer of the superior colliculus (+50%). An addnl. 15 regions displayed significant redns. in function-related glucose use ($P < .05$) in animals treated with LY354740 (30 mg/kg). LY379268 (0.1, 1.0, 10 mg/kg) produced changes in glucose metabolism in 20% of the brain regions analyzed. Significant increases ($P < .05$) in glucose use were evident in the following: the superficial layer of the superior colliculus (+81%), locus coeruleus (+57%), genu of the corpus callosum (+31%), cochlear nucleus (+26%), inferior colliculus (+20%), and the mol. layer of the hippocampus (+14%). Three regions displayed significant decreases: mammillary body (-34%), anteroventral thalamic nucleus (-28%), and the lateral habenular nucleus (-24%). These results show the important functional involvement of the limbic system together with the participation of components of different sensory systems in response to the activation of mGluR2 and mGluR3 with LY354740 and LY379268.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 91 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:454862 HCAPLUS
DOCUMENT NUMBER: 133:232757
TITLE: Characterization of [3H]-LY354740 binding to rat mGlu2 and mGlu3 receptors expressed in CHO cells using Semliki Forest virus vectors
AUTHOR(S): Schweitzer, C.; Kratzeisen, C.; Adam, G.; Lundstrom, K.; Malherbe, P.; Ohresser, S.; Stadler, H.; Wichmann, J.; Woltering, T.; Mutel, V.
CORPORATE SOURCE: Pharmaceutical Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Neuropharmacology (2000), 39(10), 1700-1706
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The binding properties of [3H]-LY354740 were characterized on rat metabotropic glutamate receptors mGlu2 and

mGlu3 expressed in Chinese hamster ovary (CHO) cells using Semliki Forest virus vectors. The saturation isotherm gave KD values of 20±5 and 53±8 nM and Bmax values of 474±161 and 667±89 fmol/mg protein for mGlu2 and mGlu3 receptors, resp. NMDA, CaCl2, DHPG and kainate were inactive up to 1 mM, whereas LY341495, DCG IV and ibotenate inhibited [3H]-LY354740 binding with similar potencies on both receptors. L-CCG I, l-AP4, l-AP5, LY354740 and 1S,3R-ACPD were 2- to 4-fold more potent inhibitors of [3H]-LY354740 binding to mGlu2 than mGlu3 receptors. However, MPPG and l-AP3 had a 6-fold and DTT a 28-fold preference for mGlu2 over mGlu3. ZnCl2, at 10 mM, inhibited more than 70% of [3H]-LY354740 binding to mGlu2 receptors. At the same concentration it did not affect significantly [3H]-LY354740 binding to mGlu3 receptors. On the contrary, glutamate, quisqualate, EGLU and NAAG showed a 3-, 5-, 7- and 12-fold preference for mGlu3 over mGlu2. Finally, GTPγS, which partially inhibited the binding on mGlu2 receptors, was inactive to inhibit [3H]-LY354740 binding on mGlu3 receptors.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 92 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:441746 HCAPLUS
DOCUMENT NUMBER: 133:58559
TITLE: Intermediates and process for producing fluorine-containing amino acid compound by using the same
INVENTOR(S): Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Tomisawa, Kazuyuki; Ito, Hisanaka; Taguchi, Takeo
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037410	A1	20000629	WO 1999-JP7096	19991217
W: AU, CA, CN, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2354619	A1	20000629	CA 1999-2354619	19991217
JP 2000239222	A	20000905	JP 1999-359789	19991217
EP 1142860	A1	20011010	EP 1999-959875	19991217
EP 1142860	B1	20040811		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 767592	B2	20031120	AU 2000-16883	19991217
AT 273267	T	20040815	AT 1999-959875	19991217
PT 1142860	T	20041130	PT 1999-959875	19991217
ES 2226472	T3	20050316	ES 1999-959875	19991217
US 6392086	B1	20020521	US 2001-857631	20010607
HK 1047430	A1	20050610	HK 2002-108913	20021206
PRIORITY APPLN. INFO.:			JP 1998-361701 A	19981218
			WO 1999-JP7096 W	19991217

OTHER SOURCE(S): CASREACT 133:58559; MARPAT 133:58559

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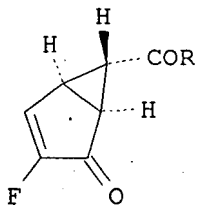

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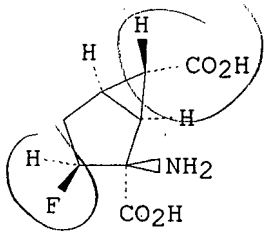

II

AB Described are (1S,5R,6S)- or (1SR,5RS,6SR)-3-fluoro-2-oxobicyclo[3.1.0]-hex-3-ene-6-carboxylic acid derivs. represented by general formula [I; R represents OR1 or NR1R2; wherein R1 and R2 are the same or different and each represents hydrogen, C1-6 alkyl, C3-6 cycloalkyl, C3-6 cycloalkyl-C1-6 alkyl, aryl, aryl-C1-6 alkyl, C1-6 alkoxy-C1-6 alkyl, C1-6 alkylthio-C1-6 alkyl or C1-6 mercaptoalkyl]; a process for producing the same; and a process for efficiently producing a fluorine-containing amino acid compound, namely (1S,2S,3S,5R,6S)- or (1SR,2SR,3SR,5RS,6SR)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (II), acting on group 2 metabotropic glutamate receptor which has therapeutic and preventive effects on psychiatric diseases or neurol. diseases (no data), characterized by hydrogenating the above compound I and then further converting the same into hydantoin or amino cyanide followed by hydrolysis. Thus, epoxidn. of Et (1S,5R,6S)-2-oxobicyclo[3.1.0]hex-2-ene-6-carboxylate with tert-Bu peroxide in the presence of benzyltrimethylammonium hydroxide in aqueous MeOH at room temperature for 20 min gave Et (1S,3R,4R,5R,6S)-3,4-epoxy-2-oxobicyclo[3.1.0]hexane-6-carboxylate which underwent fluorination with KF in ethylene glycol at 130° for 2 h to give Et (1S,5R,6S)-3-fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylate (III) and 2-hydroxyethyl (1S,5R,6S)-3-fluoro-2-oxobicyclo[3.1.0]hex-3-ene-6-carboxylate. Catalytic hydrogenation of III in the presence of 5% Pd-C in MeOH at room temperature overnight gave Et (1S,3S,5R,6S)-3-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate which was treated with ammonium carbonate and KCN in ethanol at 35° for 3 days to give Et (1S,2S,3S,5R,6S)-2-spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylate. Hydrolysis of the latter compound with 60% aqueous H2SO4 at 140° for 12 h gave (1S,2S,3S,5R,6S)-II.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 93 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:378094 HCAPLUS
DOCUMENT NUMBER: 133:129781
TITLE: Lack of effect of LY314582 (a group 2 metabotropic glutamate receptor agonist) on phencyclidine-induced locomotor activity in metabotropic glutamate receptor 2 knockout mice
AUTHOR(S): Spooren, W. P. J. M.; Gasparini, F.; van der Putten, H.; Koller, M.; Nakanishi, S.; Kuhn, R.
CORPORATE SOURCE: Novartis Pharma AG, Nervous System Research, Basel, CH-4002, Switz.

SOURCE: European Journal of Pharmacology (2000), 397(1), R1-R2
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In metabotropic glutamate receptor 2 (mGlu2) knockout mice, the group 2 metabotropic glutamate receptor agonist LY314582 (20 mg/kg, i.p.), a racemate of LY354740, inhibits neither spontaneous nor phencyclidine (PCP)-induced (2.5 mg/kg, s.c.) locomotor activity. Since LY314582 attenuated spontaneous and PCP-induced locomotor activity in wild-type control mice, these data indicate that the effects of LY314582 are mediated via the mGlu2 receptor and not via the mGlu3 receptor.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 94 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:335066 HCAPLUS
DOCUMENT NUMBER: 132:334795

TITLE: Preparation of (1S*,2S*,4R*,5R*,6S*)-2-amino-4-nitrobicyclo[3.1.0]hexane-2,6-dicarboxylic acid as excitatory amino acid receptor modulator

INVENTOR(S): Monn, James Allen; Valli, Matthew John
PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1000927	A2	20000517	EP 1999-308965	19991110
EP 1000927	A3	20000531		
EP 1000927	B1	20030604		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2350532	A1	20000525	CA 1999-2350532	19991110
WO 2000029371	A1	20000525	WO 1999-US26657	19991110
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
JP 2002529529	T	20020910	JP 2000-582359	19991110
AT 242198	T	20030615	AT 1999-308965	19991110
ES 2200474	T3	20040301	ES 1999-308965	19991110
US 6143783	A	20001107	US 1999-438764	19991111
PRIORITY APPLN. INFO.:			US 1998-108371P P	19981113
			WO 1999-US26657 W	19991110

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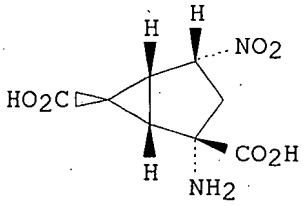

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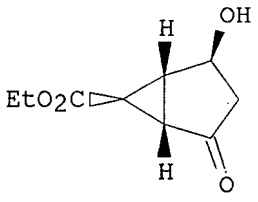

II

AB Title bicyclic compound I or its non-toxic metabolically labile ester and amides or pharmaceutically acceptable salts were prepared as modulators of metabotropic glutamate receptor function.
Thus, cyclopropanation of 2-cyclopenten-1-one with (carbethoxymethyl)dimethylsulfonium bromide (preparation given) gave 68% (1S*,5R*,6S*)-Et 2-oxobicyclo[3.1.0]hexane-6-carboxylate, which was converted into hydroxy derivative II via silyl enol ether formation, oxidation to
the corresponding α,β-unsatd. ketone, epoxidn., and ring opening. II was converted into final product I in 7 addnl. steps.

L9 ANSWER 95 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:256024 HCAPLUS
DOCUMENT NUMBER: 133:13023
TITLE: Pharmacological characterization of the rat metabotropic glutamate receptor type 8a revealed strong similarities and slight differences with the type 4a receptor
AUTHOR(S): De Colle, C.; Bessis, A.-S.; Bockaert, J.; Acher, F.; Pin, J.-P.
CORPORATE SOURCE: Centre INSERM-CNRS de Pharmacologie-Endocrinologie, UPR 9023-CNRS, Montpellier, 34094, Fr.
SOURCE: European Journal of Pharmacology (2000), 394(1), 17-26
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the brain, group-III metabotropic glutamate (mGlu) receptors mGlu4, mGlu7 and mGlu8 receptors play a critical role in controlling the release process at many glutamatergic synapses. The pharmacol. profile of mGlu4 receptor has been studied extensively, allowing us to propose a pharmacophore model for this receptor subtype. Surprisingly, the activity of only a few compds. have been reported on mGlu7 and mGlu8 receptors. In order to identify new possibilities for the design of selective compds. able to discriminate between the members of the group-III mGlu receptors, we have undertaken a complete pharmacol. characterization of mGlu8 receptor and compared it with that of mGlu4 receptor, using the same expression system, and the same read out. The activities of 32 different mols. revealed that these two mGlu receptors subtypes share a similar pharmacol. profile. Only small differences were noticed in addition to that previously reported with S-carboxyglutamate (S-Gla) being a partial agonist at mGlu4 receptor and a full antagonist at mGlu8 receptor. These include: a slightly higher relative potency of the agonists 1S,3R and 1S,3S-aminocyclopentane-1,3-dicarboxylic acid (ACPD), S-4-carboxyphenylglycine (S-4CPG) and S-4-carboxy-3-hydroxyphenylglycine (S-4C3HPG), and a slightly higher potency of the antagonists LY 354740 and

RS-α-methyl-4-phosphonophenylglycine (MPPG) on mGlu8 receptor. When superimposed on the mGlu4 receptor pharmacophore model, these mols. revealed three regions that may be different between the ligand binding sites of mGlu8 and mGlu4 receptors.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 96 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:236783 HCAPLUS
DOCUMENT NUMBER: 133:84153
TITLE: LY354740, a potent group II metabotropic glutamate receptor agonist prevents lactate-induced panic-like response in panic-prone rats
AUTHOR(S): Shekhar, A.; Keim, S. R.
CORPORATE SOURCE: Institute of Psychiatric Research, Pharmacology and Toxicology and Program in Medical Neurobiology, Departments of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA
SOURCE: Neuropharmacology (2000), 39(7), 1139-1146
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LY354740 is a potent and selective agonist at the group II metabotropic glutamate receptors and is shown to be an effective inhibitor of glutamate release with significant anxiolytic and drug withdrawal alleviating properties in certain animal models. Rats with chronic inhibition of GABA synthesis in the dorsomedial hypothalamus (DMH) are highly anxious and exhibit panic-like responses to peripheral lactate infusions similar to patients with panic disorder. Using these panic-prone rats, we tested the efficacy of LY354740 in preventing the lactate-induced panic-like response, comparing it to alprazolam, a clin. effective anti-panic drug. Rats were fitted with femoral arterial and venous catheters and implanted with Alzet pumps infusing the GABA synthesis inhibitor l-allylglycine into the DMH. After four days of recovery, they were confirmed to be panic-prone to lactate infusions as indicated by increases in heart rate, blood pressure, respiratory rate and "anxiety" measured in the social interaction test. Next, they were pretreated with either vehicle, LY354740 (0.3 and 0.6 mg/kg) or alprazolam (0.5 and 1.0 mg/kg) and re-challenged with lactate infusions. LY354740 treatment was equally efficacious as alprazolam in preventing lactate-induced panic attacks in this model. These data suggest that LY354740 could be a novel anti-panic drug, as effective as alprazolam in acute treatment.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 97 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:236781 HCAPLUS
DOCUMENT NUMBER: 133:69122
TITLE: Conservation of the ligand recognition site of metabotropic glutamate receptors during evolution
AUTHOR(S): Parmentier, M.-L.; Galvez, T.; Acher, F.; Peyre, B.; Pellicciari, R.; Grau, Y.; Bockaert, J.; Pin, J.-P.
CORPORATE SOURCE: Centre INSERM-CNRS de Pharmacologie-Endocrinologie,

UPR 9023-CNRS, Montpellier, 34094, Fr.
SOURCE: Neuropharmacology (2000), 39(7), 1119-1131
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mammalian metabotropic glutamate receptors (mGluRs) are classified into 3 groups based on their sequence similarity and ligand recognition selectivity. Recently, we identified a Drosophila mGluR (DmGluAR) which is about equidistant, phylogenetically, from the 3 mGluR groups. However, both the G-protein coupling selectivity and the pharmacol. profile of DmGluAR, as analyzed with mutated G-proteins and a few compds., look similar to those of mammalian group-II mGluRs. In the present study we carefully examined the pharmacol. profile of DmGluAR, and compared it to those of the rat mGlu1a, mGlu2 and mGlu4a receptors, representative of group-I, II and III resp. The pharmacol. profile of DmGluAR was found to be similar to that of mGlu2R, and only very small differences could be identified at the level of their pharmacophore models. These data strongly suggest that the binding sites of these two receptors are similar. To further document this idea, a 3D model of the mGlu2 binding domain was constructed based on the low sequence similarity with periplasmic amino acid binding proteins, and was used to identify the residues that possibly constitute the ligand recognition pocket. Interestingly, this putative binding pocket was found to be very well conserved between DmGluAR and the mammalian group-II receptors. These data indicate that there has been a strong selective pressure during evolution to maintain the ligand recognition selectivity of mGluRs.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 98 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:211432 HCAPLUS
DOCUMENT NUMBER: 132:274253

TITLE: Roles of group II metabotropic glutamate receptors in modulation of seizure activity

AUTHOR(S): Klodzinska, A.; Bijak, M.; Chojnacka-Wojcik, E.; Kroczka, B.; Swiader, M.; Czuczwar, S. J.; Pilc, A.
CORPORATE SOURCE: Institute of Pharmacology, Polish Academy of Sciences, Krakow, PL-31-343, Pol.

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2000), 361(3), 283-288
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Evidence suggests that metabotropic glutamate receptors (mGluR) are involved in mediating seizures and epileptogenesis. In the present expts., the selective, group II mGluR agonist LY 354740 (0.1-1.0 μM) inhibited spontaneous epileptiform discharges which developed in rat cortical slices in Mg2+-free medium. LY 354740 (4-16 mg/kg) administered prior to an injection of pentylenetetrazol (80 mg/kg) or picrotoxin (3.2 mg/kg) produced a dose-dependent decrease in the number of mice exhibiting clonic convulsions, but had no effect on NMDA (150 mg/kg)-induced convulsions. LY 354740 (4-16 mg/kg) did not affect lethality induced in mice by pentylenetetrazol, picrotoxin or NMDA. LY 354740 potentiated the

anticonvulsant activity of the conventional antiepileptic drug diazepam, significantly decreasing the ED50 for that drug's effect on pentylenetetrazol-induced convulsions by 30%, but had no influence on anticonvulsant activity of ethosuximide and valproic acid. A pharmacokinetic interaction between LY 354740 and diazepam, leading to the lowering of the plasma level of free diazepam, was also demonstrated. Our data suggest that the group II mGluR agonist LY 354740 possesses antiseizure activity and may modify the effects of some conventional antiepileptic drugs.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 99 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:161245 HCAPLUS
DOCUMENT NUMBER: 132:208130
TITLE: Preparation of aminofluorobicyclohexanedicarboxylic acid derivatives as group-2 metabotropic glutamate receptor agonists
INVENTOR(S): Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Tomisawa, Kazuyuki
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000012464	A1	20000309	WO 1999-JP3984		19990726
W: AU, CA, CN, KR, US					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2341865	A1	20000309	CA 1999-2341865		19990726
CA 2341865	C	20060117			
AU 9948007	A1	20000321	AU 1999-48007		19990726
AU 746806	B2	20020502			
JP 2000336071	A	20001205	JP 1999-211398		19990726
EP 1110943	A1	20010627	EP 1999-931532		19990726
EP 1110943	B1	20040616			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
AT 269293	T	20040715	AT 1999-931532		19990726
PT 1110943	T	20040831	PT 1999-931532		19990726
ES 2222715	T3	20050201	ES 1999-931532		19990726
US 6333428	B1	20011225	US 2001-763408		20010222
HK 1049996	A1	20060915	HK 2003-102289		20030331
PRIORITY APPLN. INFO.:			JP 1998-246343	A	19980831
			JP 1999-82607	A	19990325
			WO 1999-JP3984	W	19990726

OTHER SOURCE(S): MARPAT 132:208130
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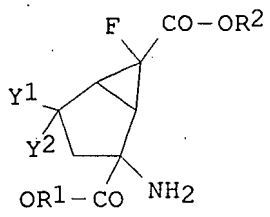

I

AB The title compds. I [R1 and R2 represent each hydrogen, alkyl, cycloalkyl, etc.; and Y1 and Y2 represent each hydrogen, alkylthio, cycloalkylthio, alkoxy, etc., or one of Y1 and Y2 represents hydrogen and the other represents hydroxy, alkoxy, cycloalkoxy, etc., or Y1 and Y2 together represent oxygen or X(CH2)nX (wherein X represents oxygen or sulfur; and n is 2 or 3)] are prepared These compds. are useful as drugs for treating and preventing psychiatric disorders such as schizophrenia, anxiety, depression and bipolar disturbance, and neurol. diseases such as drug addiction, cognition disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease, movement disorder in association with muscular rigidity, brain ischemia, brain insufficiency, spinal cord lesion and head disorder. (1RS,2SR,5RS,6RS)-2-Amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid in vitro showed ED50 of 34.2 nM in suppressing the accumulation of cAMP in CHO cells expressing mGluR2 receptor.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 100 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:157966 HCAPLUS
DOCUMENT NUMBER: 132:166520
TITLE: Stereospecific synthesis of 2-amino-bicyclo[3.1.0]hexan-2,6-dicarboxylic acid derivatives for use as metabotropic glutamate receptor ligands
INVENTOR(S): Adam, Geo; Huguenin-Virchaux, Philippe Nicolas; Mutel, Vincent; Stadler, Heinz; Woltering, Thomas Johannes
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19941675	A1	20000309	DE 1999-19941675	19990901
CH 694053	A5	20040630	CH 1999-1550	19990824
US 6107342	A	20000822	US 1999-385935	19990830
CA 2281272	A1	20000303	CA 1999-2281272	19990831
GB 2341179	A	20000308	GB 1999-20579	19990831
GB 2341179	B	20040218		
JP 2000086597	A	20000328	JP 1999-244167	19990831
JP 3340409	B2	20021105		
SE 9903088	A	20000304	SE 1999-3088	19990901
SE 520026	C2	20030513		
FR 2786768	A1	20000609	FR 1999-10971	19990901

FR 2786768	B1	20041015			
IT 99MI1860	A1	20010301	IT 1999-MI1860		19990901
IT 1313618	B1	20020909			
NL 1012963	A1	20000306	NL 1999-1012963		19990902
NL 1012963	C2	20031023			
AU 9947327	A1	20000316	AU 1999-47327		19990902
AU 757939	B2	20030313			
AT 501853	A1	20061115	AT 1999-1514		19990902
BE 1014616	A3	20040203	BE 1999-595		19990903
PRIORITY APPLN. INFO.:			EP 1998-116670	A	19980903

OTHER SOURCE(S): MARPAT 132:166520
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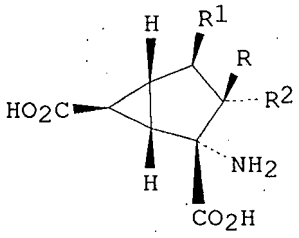

I

AB Title compds. [(I); R = OH, alkoxy, alkenyloxy, PhCH2O-, H, 2H, 3H; R1 = H, 3H; R,R1 = bond; R2 = H, 2H, 3H, OH, NH2] were stereospecifically prepared for use in treatment of neurol. conditions and psychiatric disturbances (no data). Thus, racemic Et (1α,5α,6α)-2-oxo-bicyclo[3.1.0]hexane-6-carboxylic acid was reacted with Ph bis((trifluoromethyl)sulfonyl)amine and the resulting triflate transformed into the racemic 2-ethyl-6-benzyl bicyclo[3.1.0]hex-2-ene-2,6-dicarboxylic acid, reaction of which with K2[OsO2(OH)4] gave stereospecifically the 1S,2S,3R,6S-diol, which could be isolated in 26% yield, at >99% enantiomeric excess. Preparation of the 2R-2-azido compound from the diol through a cyclic sulfate gave an intermediate which could then be alkylated, aminated, hydrogenated, de-esterified, or otherwise treated to give I, for use as ligands for metabotropic glutamate group II receptors.

L9 ANSWER 101 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:150484 HCAPLUS
DOCUMENT NUMBER: 132:203150
TITLE: 4-Substituted-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as metabotropic glutamate receptor agonists and their compositions
INVENTOR(S): Nakazato, Atsuo; Kumagaya, Toshihito; Sakagami, Kazunari; Tomizawa, Kazuyuki
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

JP 2000072731	A	20000307	JP 1998-246344	19980831
PRIORITY APPLN. INFO.:			JP 1998-246344	19980831
OTHER SOURCE(S):	MARPAT 132:203150			

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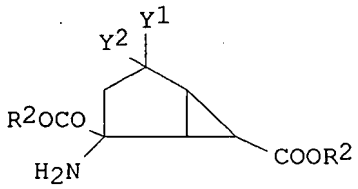

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AB The derivs. I [Y1, Y2 = C1-10 alkylthio or Y1 and Y2 are bonded together to form S(CH2)nS (n = 2, 3) or Y1Y2 represents :O; R1, R2 = H, C1-10 alkyl] or their pharmaceutically acceptable salts, and pharmaceutical compns. containing I or their salts are claimed. I act on group 2 metabotropic glutamate receptor mGluR2/mGluR3 and are useful for treatment of schizophrenia, anxiety, depression, bipolar disorders, epilepsy, drug dependence, cognition disorders, Alzheimer's disease, Huntington's chorea, parkinsonism, etc. (+)-(1S*,2R*,5R*,6R*)-2-amino-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (preparation given) suppressed forskolin-induced accumulation in CHO cells stably expressing mGluR2 at ED50 0.736 nM, vs. 18.74 nM for LY 354740.

L9 ANSWER 102 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2000:97067 HCAPLUS
DOCUMENT NUMBER:	133:12655
TITLE:	Selective group II glutamate metabotropic receptor agonist LY354740 attenuates pentetrazole- and picrotoxin-induced seizures
AUTHOR(S):	Klodzinska, Aleksandra; Chojnacka-Wojcik, Ewa; Pilc, Andrzej
CORPORATE SOURCE:	Institute of Pharmacology, Polish Academy of Sciences, Krakow, PL 31-343, Pol.
SOURCE:	Polish Journal of Pharmacology (1999), 51(6), 543-545 CODEN: PJPAE3; ISSN: 1230-6002
PUBLISHER:	Polish Academy of Sciences, Institute of Pharmacology
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB There are several data indicating the involvement of metabotropic glutamate receptors (mGluR) in seizures and epileptogenesis. In the present expts., the selective group II mGluR agonist (+)-2-aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid (LY 354740) at doses from 4 to 16 mg/kg) administered prior to the injection of pentetrazole (80 mg/kg) or picrotoxin (3.2 mg/kg) produced a dose-dependent decrease in the number of mice exhibiting clonic convulsions. Our data suggest that group II mGluR agonist LY 354740 possesses antiseizure activity.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 103 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:74530 HCAPLUS
DOCUMENT NUMBER: 132:217391
TITLE: Neuroprotective actions of novel and potent ligands of group I and group II metabotropic glutamate receptors
AUTHOR(S): Kingston, A. E.; O'Neill, M. J.; Bond, A.; Bruno, V.; Battaglia, G.; Nicoletti, F.; Harris, J. R.; Clark, B. P.; Monn, J. A.; Lodge, D.; Schoepp, D. D.
CORPORATE SOURCE: Eli Lilly and Co. Ltd., Windlesham, Surrey, GU20 6PH, UK
SOURCE: Annals of the New York Academy of Sciences (1999), 890(Neuroprotective Agents), 438-449
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of group I metabotropic glutamate (mGlu) receptors in neurodegeneration is controversial because of the contradictory effects of mGlu1/5 agonists in in vitro models of neuronal cell death. In this study, novel and selective antagonists of mGlu1 and mGlu5: LY367385 and LY367366 were found to show consistent neuroprotective effects against N-methyl-D-aspartate (NMDA)-induced excitotoxicity in vitro and in vivo. Furthermore, intraventricular administration of LY367385 reduced hippocampal cell death in gerbils subjected to transient global ischemia. Previous studies have also shown that activation of group II mGlu receptors may contribute to neuroprotective mechanisms in vitro and in vivo. Three potent group II mGlu agonists-LY354740, LY379268 and LY389795-were found to attenuate both NMDA excitotoxicity and staurosporine-induced neuronal cell death. LY354740 and LY379268 were protective against transient global ischemia in gerbils when dosed i.p. These results support the view that antagonists of mGlu1 and mGlu5 and agonists of group II mGlu receptors may be useful agents in the therapeutic treatment of neurodegenerative disease.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

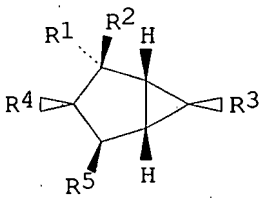
L9 ANSWER 104 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:68447 HCAPLUS
DOCUMENT NUMBER: 132:93652
TITLE: Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylates and related compounds as pharmaceutical intermediates and modulators of metabotropic glutamate receptor function.
INVENTOR(S): Baker, Stephen Richard; Monn, James Allen; Ezquerra Carrera, Jesus; Dominguez Fernandez, Carmen
PATENT ASSIGNEE(S): Eli Lilly and Company Limited, UK; Lilly, S.A.; Eli Lilly and Company
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000004010	A1	20000127	WO 1999-GB2273 19990714
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2338054	A1	20000127	CA 1999-2338054 19990714
AU 9949223	A1	20000207	AU 1999-49223 19990714
EP 1097149	A1	20010509	EP 1999-933048 19990714
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 2002520406	T	20020709	JP 2000-560116 19990714
PRIORITY APPLN. INFO.:			GB 1998-15542 A 19980717
			WO 1999-GB2273 W 19990714

OTHER SOURCE(S): MARPAT 132:93652

GI



I

AB Title compds. [I; either R1 = N3, (protected) amino; R2 = (protected) carboxy; or R1 = trihalomethyl; R2 = OH; R3 = (protected) carboxy; either R4 = OR6 and R5 = OR7; or R4 and R5 = H or R4R5 = bond; ether R6 and R7 = H; or R6R7 = diol protecting group; provided that when R4 and R5 = H, R1 ≠ amino], were prepared s pharmaceutical intermediates and modulators of metabotropic glutamate receptor function (no data). Thus, ethoxycarbonylmethyldimethylsulfonium bromide in CHCl3 was treated with DBU and then with (-)-2,3-(cyclohexylidenedioxy)-4-cyclopentenone in CHCl3 followed by stirring overnight to give 96% Et (1S,3R,4R,5R,6S)-2-oxo-3,4-cyclohexylidenedioxybicyclo[3.1.0]hexane-6-carboxylate. This with CHCl3 in THF at -78° was treated with Li hexamethyldisilazide in THF followed by warming to room temperature to give 94% Et (1S,2S,3R,4R,5R,6S)-2-trichloromethyl-2-hydroxy-3,4-cyclohexylidenedioxybicyclo[3.1.0]hexane-6-carboxylate. Treatment of the latter with NaN3, 18-crown-6, and DBU in MeOH over 6 h gave 84% di-Me (1S,2R,3S,4R,5R,6S)-2-azido-3,4-cyclohexylidenedioxybicyclo[3.1.0]hexane-2,6-dicarboxylate. This was hydrogenated in EtOAc over Pd/C to give 71% of the corresponding amine, which was converted to (1S,2R,3S,4R,5R,6R)-2-amino-3,4-dihydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid in several steps.

L9 ANSWER 105 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:17547 HCAPLUS
DOCUMENT NUMBER: 132:147023
TITLE: Physiological antagonism between 5-hydroxytryptamine2a and group II metabotropic glutamate receptors in prefrontal cortex
AUTHOR(S): Marek, Gerard J.; Wright, Rebecca A.; Schoepp, Darryle D.; Monn, James A.; Aghajanian, George K.
CORPORATE SOURCE: Departments of Psychiatry and Pharmacology, Yale University School of Medicine, Ribicoff Research Facilities of the Connecticut Mental Health Center, New Haven, CT, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(1), 76-87
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In prefrontal cortex, 5-hydroxytryptamine2A (5-HT2A) receptors have been linked to the action of hallucinogens and atypical antidepressant/antipsychotic drugs. Previously, the authors have shown in cortical layer V pyramidal cells that a nonselective metabotropic glutamate (mGlu) receptor agonist suppresses the induction of excitatory postsynaptic potentials/currents (EPSPs/EPSCs) via activation of 5-HT2A receptors. In this study, the authors tested the ability of the selective mGlu2/3 agonist (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate (LY354740) and the selective mGlu2/3 antagonist 2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3(xanthyl-9 -yl)propanoic acid (LY341495) to modulate serotonin(5-HT)-induced EPSPs and elec. evoked EPSPs by using intracellular recording from layer V pyramidal cells in medial prefrontal cortex. The mGlu2/3 antagonist LY341495 increased the frequency and amplitude of 5-HT-induced EPSCs, suggesting a role for mGlu2/3 receptors in mediating the action of endogenous glutamate on autoreceptors. Conversely, the mGlu2/3 agonist LY354740 was highly effective and potent (EC50 = 89 nM) in suppressing glutamate release induced by 5-HT2A receptor activation in the medial prefrontal cortex, probably via a presynaptic mechanism. The mGlu2/3 antagonist LY341495 potently blocked the suppressant effect of LY354740 on 5-HT-induced EPSCs as well as elec. evoked early EPSPs. Autoradiog. with the radioligands [3H]LY354740 and [125I](±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane shows a striking overlap of the laminar distribution of mGlu2/3 and 5-HT2A receptors in the medial prefrontal cortex that is not apparent in other cortical regions. These findings suggest a close coupling between mGlu2/3 and 5-HT2A receptors in the prefrontal cortex that may be relevant for novel therapeutic approaches in the treatment of neuropsychiatric syndromes such as depression and schizophrenia.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 106 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:653043 HCAPLUS
DOCUMENT NUMBER: 132:146513
TITLE: The retention deficit induced by (RS)-α-methyl-4-carboxyphenylglycine in a lever-press learning task is blocked by selective agonists of either group I or group II metabotropic glutamate receptors

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

AUTHOR(S): Mathis, C.; Ungerer, Arielle
CORPORATE SOURCE: URA 1295, Laboratoire d'Ethologie et de Neurobiologie, Universite Louis Pasteur, Strasbourg, F-67000, Fr.
SOURCE: Experimental Brain Research (1999), 129(1), 147-155
CODEN: EXBRAP; ISSN: 0014-4819
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of immediate post-training administration of drugs interacting with group I and/or group II glutamate metabotropic receptors (mGluRs) were determined on the retention performance of a partially acquired lever-press learning task in mice. The antagonist (RS)-α-methyl-4-carboxyphenylglycine (MCPG) dose-dependently (0.1-100 nmol/mouse, i.c.v.) impairs the retention performance evaluated 24 h post-training. The retention deficit induced by 100 nmol MCPG is related to the selective suppression of a time-dependent spontaneous improvement of performance between the 2 sessions. This phenomenon appears progressively within 24 h post-training in control mice and is thought to reflect post-training processing of memory traces. The coadministration of either (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), the group I mGluR agonist (R,S)3,5-dihydroxyphenylglycine (DHPG), or the group II mGluR agonist LY354740, completely blocked MCPG-induced deficits at a dose of 0.1 nmol for each agonist. These results suggest that selective activation of either group I or group II mGluRs is able to prevent the memory retention deficits induced by MCPG.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 107 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:637913 HCAPLUS
DOCUMENT NUMBER: 132:18876
TITLE: LY354740: A systemically active mGlu2/mGlu3 receptor agonist
AUTHOR(S): Schoepp, Darryle D.; Monn, James A.; Marek, Gerard J.; Aghajanian, George; Moghaddam, Bita
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: CNS Drug Reviews (1999), 5(1), 1-12
CODEN: CDREFB; ISSN: 1080-563X
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 51 refs., on in vitro and in vivo pharmacol. properties of LY354740, a highly potent and selective agonist for group II mGLuR2 and mGluR3 receptors. LY354740 represents a novel pharmacol. agent to explore the therapeutic applications of modulating glutamate neurotransmission by activating group II mGLu receptors in vivo. LY354740 also showed activity in certain benzodiazepine-sensitive models of fear/anxiety in animals without the secondary pharmacol. observed with other anxiolytics. LY354740 suppresses withdrawal phenomena associated with diazepam, nicotine, and morphine in rats. LY354740 selectively suppresses release of glutamate and behavioral disruptions subsequent to PCP administration in rats. LY354740 protects against excitotoxic injury to neurons in vitro and provides some protection against traumatic and ischemic injury to neurons.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 108 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:632716 HCAPLUS
DOCUMENT NUMBER: 132:331
TITLE: The metabotropic glutamate 2/3 receptor agonists LY354740 and LY379268 selectively attenuate phencyclidine versus d-amphetamine motor behaviors in rats
AUTHOR(S): Cartmell, Jayne; Monn, James A.; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 291(1), 161-170
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous animal studies have indicated that drugs targeted at metabotropic glutamate (mGlu) receptors may be useful for treatment of psychosis. In this article, the effects of the novel, potent, and selective mGlu2/3 receptor agonists LY354740 and LY379268, and the clin. effective agents clozapine and haloperidol, were investigated using phencyclidine (PCP; 5 mg/kg)- vs. d-amphetamine (AMP; 3 mg/kg)-evoked motor activities. LY354740 (1-10 mg/kg s.c.), LY379268 (0.3-3 mg/kg s.c.), clozapine (1-10 mg/kg s.c.), and haloperidol (0.03-1 mg/kg s.c.) reversed the increases in ambulations, fine motor (nonambulatory) movements, and decreased time at rest evoked by PCP. Furthermore, the inhibitions of the PCP response by the mGlu2/3 agonist LY379268, but not by clozapine, were completely reversed by the selective mGlu2/3 receptor antagonist LY341495. Doses of LY354740 and LY379268 that blocked the effects on PCP had no effects on rotorod performance, and (with the exception of rearing behavior) had minimal effects on AMP-evoked motor activities. Clozapine blocked AMP-induced rearing but enhanced AMP-induced ambulations and fine movements at the lower doses (1 and 3 mg/kg). Unlike the mGlu2/3 agonists, the highest dose of clozapine tested (10 mg/kg) impaired animals on the rotorod. Haloperidol potently blocked all PCP and AMP effects, but only at doses associated with motor impairment. These data demonstrate that mGlu2/3 receptor agonists act via a unique mechanism to selectively block PCP-induced behaviors. Moreover, the marked mGlu2/3 receptor-mediated inhibitions of PCP-evoked behaviors by LY354740 and LY379268, with minimal effects on AMP, may indicate potential antipsychotic effects in humans in the absence of dopamine mediated extrapyramidal side effects.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 109 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:581444 HCAPLUS
DOCUMENT NUMBER: 132:322
TITLE: Selective activation of group II mGluRs with LY354740 does not prevent neuronal excitotoxicity
AUTHOR(S): Behrens, M. M.; Strasser, U.; Heidinger, V.; Lobner, D.; Yu, S.-P.; McDonald, J. W.; Won, M.; Choi, D. W.
CORPORATE SOURCE: Center for the Study of Nervous System Injury and Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA
SOURCE: Neuropharmacology (1999), 38(10), 1621-1630
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent reports have suggested a role for group II metabotropic glutamate receptors (mGluRs) in the attenuation of excitotoxicity. Here we examined the effects of the recently available group II agonist (+)-2-Aminobicyclo[3.1.0]hexane-2-6-dicarboxylic acid (LY354740) on N-methyl-d-aspartate (NMDA)-induced excitotoxic neuronal death, as well as on hypoxic-ischemic neuronal death both in vitro and in vivo. At concns. shown to be selective for group II mGluRs expressed in cell lines (0.1-100 nM), LY354740 did not attenuate NMDA-mediated neuronal death in vitro or in vivo. Furthermore, LY354740 did not attenuate oxygen-glucose deprivation-induced neuronal death in vitro or ischemic infarction after transient middle cerebral artery occlusion in rats. In addition, the neuroprotective effect of another group II agonist, (S)-4-carboxy-3-phenylglycine (4C3HPG), which has shown injury attenuating effects both in vitro and in vivo, was not blocked by the group II antagonists (2 S)-α-ethylglutamic acid (EGLU), (RS)-α-methyl-4-sulfonophenylglycine (MSPG), or the group III antagonist (S)-α-methyl-3-carboxyphenylalanine (MCPA), suggesting that this neuroprotection may be mediated by other effects such as upon group I mGluRs.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 110 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:546800 HCAPLUS
DOCUMENT NUMBER: 131:281408
TITLE: Neuroprotection by metabotropic glutamate receptor agonists: LY354740, LY379268 and LY389795
AUTHOR(S): Kingston, Ann E.; O'Neill, Michael J.; Lam, Amy; Bales, Kelly R.; Monn, James A.; Schoepp, Darryle D.
CORPORATE SOURCE: Eli Lilly, Lilly Research Centre, Windleshanz, Surrey, GU20 6PH, UK
SOURCE: European Journal of Pharmacology (1999), 377(2/3), 155-165
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rat cortical neuronal cultures, metabotropic glutamate (mGlu) receptor agonists: LY354740 (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate; LY379268 (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate, and LY389795 (-)-2-thia-4-aminobicyclo[3.1.0]- hexane-4,6-dicarboxylate, were neuroprotective against toxicity induced by N-methyl-D-aspartic acid (NMDA), kainic acid and staurosporine as measured by release of lactate dehydrogenase (LDH) activity into culture supernatants and DNA fragmentation by oligonucleosome formation. The potencies of the agonists were at least 100 times greater in reducing nucleosome formation than LDH release indicating a differential effect on neurons dying by apoptosis than by necrosis. In vivo studies showed that LY354740 was able to mediate a partial protection against apoptosis in CA1 hippocampal cells under ischemic conditions where substantial CAI cell loss occurred. The effects of the agonists in vitro were: (a) reversed by mGlu receptor antagonist LY341495, (b) enhanced by the presence of glial cells, (c) abrogated by RNA and protein synthesis inhibitors, and (d) unaltered by

inhibition of endogenous adenosine activity. These results suggest that group 11 mGlu receptor agonists may represent a novel therapeutic strategy for the treatment of neurodegenerative diseases.

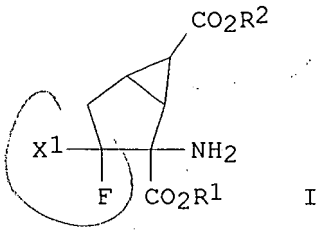
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 111 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:495267 HCAPLUS
DOCUMENT NUMBER: 131:130284
TITLE: Preparation of fluorine-containing amino acid derivatives as group-2 metabotropic glutamate receptor agonists
INVENTOR(S): Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Tomisawa, Kazuyuki
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9938839	A1	19990805	WO 1999-JP324	19990127
W: AU, CA, CN, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9921835	A	19990816	AU 1999-21835	19990127
AU 734812	B2	20010621		
CA 2318800	A1	19990825	CA 1999-2318800	19990127
CA 2318800	C	20051220		
JP 11279129	A	19991012	JP 1999-19137	19990127
EP 1052246	A1	20001115	EP 1999-901877	19990127
EP 1052246	B1	20030402		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 236118	T	20030415	AT 1999-901877	19990127
PT 1052246	T	20030630	PT 1999-901877	19990127
ES 2191412	T3	20030901	ES 1999-901877	19990127
US 6316498	B1	20011113	US 2000-601131	20000727
HK 1036792	A1	20050603	HK 2001-107767	20011106

PRIORITY APPLN. INFO.: JP 1998-15444 A 19980128
WO 1999-JP324 W 19990127

OTHER SOURCE(S): MARPAT 131:130284
GI



I

AB Fluorine-containing amino acid derivs. represented general formula (I), pharmaceutically acceptable salts thereof or hydrates of the same (wherein X1 represents hydrogen or fluorine; and R1 and R2 are the same or different and each represents hydrogen or lower C1-10 alkyl) are prepared. These compds. are useful as drugs, in particular, group 2 metabotropic glutamate receptor agonists for treating and preventing psychiatric disorders such as schizophrenia, anxiety, and their associated diseases, depression, dipolar disturbance, and epilepsy, and neurol. diseases such as drug addiction, cognition disorder, Alzheimer's disease, Huntington's chorea, Parkinson's disease, motility disturbance associating muscular stiffness, cerebral ischemia, cerebral insufficiency, spinal cord lesion, and head disorders. Thus, optical resolution of (1SR,2SR,3SR,5RS,6SR)-2-spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic acid by formation of the diastereomeric salt with (R)-(+)-1-phenylethylamine followed by acidification of the salt with aqueous HCl to gave (1S,2S,3S,5R,6S)-2-spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic acid which was heated with 60% aqueous H_2SO_4 at 140° for 2 days to give (1S,2S,3S,5R,6S)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (II). II in vitro showed ED50 of 23.65 nM for suppressing the accumulation of cAMP in CHO cells expressing mGluR2 metabotropic receptor.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 112 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:465812 HCAPLUS
DOCUMENT NUMBER: 131:222997
TITLE: Pharmacophore Models of Group I and Group II Metabotropic Glutamate Receptor Agonists. Analysis of Conformational, Steric, and Topological Parameters Affecting Potency and Selectivity
AUTHOR(S): Costantino, Gabriele; Macchiarulo, Antonio; Pellicciari, Roberto
CORPORATE SOURCE: Istituto di Chimica e Tecnologia del Farmaco, Perugia, I-06123, Italy
SOURCE: Journal of Medicinal Chemistry (1999), 42(15), 2816-2827
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A wide variety of conformationally constrained glutamate analogs, active as group I or group II metabotropic glutamate receptor agonists, were employed in a mol. modeling study aimed at the definition of group I and group II agonist pharmacophoric models. The results of this study can be summarized as follows: (i) Recognition sites of both group I and group II mGluRs can adequately be described by five-point pharmacophores. (ii) An extended conformation of glutamate is required for interaction with both group I and group II mGluRs. Group I receptors, however, can also be activated by a more folded conformation if only four pharmacophore points are considered. (iii) Conformational preferences are, however, not sufficient to explain the potency and selectivity of the whole set of ligands. Volume comparison anal. allowed us to define steric environments for group I and group II mGluRs. Group I mGluRs are characterized by a region of allowed volume in proximity of the

distal acidic function, whereas group II mGluRs are characterized by a small polar pocket whose occupancy confers high potency and selectivity. Finally, our study points out the necessity of a careful anal. of the energetic requirements needed to attain the putative bioactive conformations and of explicitly considering the conformational mobility of carboxylate groups.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 113 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:416112 HCAPLUS
DOCUMENT NUMBER: 131:179629
TITLE: Group II metabotropic glutamate receptor activation attenuates traumatic neuronal injury and improves neurological recovery after traumatic brain injury
AUTHOR(S): Allen, Jason W.; Ivanova, Svetlana A.; Fan, Lei; Espey, Michael G.; Basile, Anthony S.; Faden, Alan I.
CORPORATE SOURCE: Institute for Cognitive and Computational Sciences and Interdisciplinary Program in Neuroscience, Georgetown University Medical Center, Washington, DC, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 290(1), 112-120
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors examined the effects of modulating group II metabotropic glutamate receptors (mGluRs) on traumatic neuronal injury using both in vitro and in vivo models. Treatment with various selective group II mGluR agonists significantly decreased lactate dehydrogenase release, a marker of cell death, after traumatic injury to rat neuronal-glial cultures; injury-induced increases in cAMP and glutamate levels were also significantly reduced by a group II agonist. The neuroprotective effects of group II agonists were markedly attenuated by co-administration of a group II antagonist or a membrane-permeable cAMP analog and were additive to those provided by an N-methyl-D-aspartate receptor antagonist or a selective group I mGluR antagonist. Administration of a group II mGluR agonist 30 min after lateral fluid percussion-induced brain injury in rats significantly improved subsequent behavioral recovery as compared with vehicle-treated controls. Together these studies indicate that group II mGluR agonists protect against traumatic neuronal injury by attenuating glutamate release and cAMP levels and suggest a potential role for these agents in the treatment of clin. neurotrauma.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 114 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:405962 HCAPLUS
DOCUMENT NUMBER: 131:182627
TITLE: DmGluRA, a Drosophila metabotropic glutamate receptor, activates G-protein inwardly rectifying potassium channels in Xenopus oocytes
AUTHOR(S): Raymond, Valerie; Hamon, Alain; Grau, Yves; Lapied,

Bruno
CORPORATE SOURCE: UPRES EA 2647, Laboratoire de Neurophysiologie, Universite d'Angers, Angers, F-49045, Fr.
SOURCE: Neuroscience Letters (1999), 269(1), 1-4
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Xenopus oocytes were coinjected with cDNAs encoding the D. melanogaster metabotropic glutamate receptor (DmGluRA) and 2 mammalian G-protein inwardly rectifying K+ channel subunits (GIRK1 and GIRK2). Glutamate and 2 vertebrate group II mGluR agonists (order of potency: LY 354740 > glutamate > DCG IV) elicited inwardly rectifying K+ currents. These inward currents were sensitive to cesium and barium. They were also blocked by 2 group II specific antagonists MCCG and APICA (IC50s 97.5 and 200 μM, resp.) and not affected by a group I antagonist (AIDA). Finally, the A-protomer of PTX reduced the glutamate-induced GIRK currents. This study is the 1st characterization of an invertebrate mGluR-mediated GIRK currents via a PTX-sensitive G protein.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 115 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:390050 HCAPLUS
DOCUMENT NUMBER: 131:180145

TITLE: Effects of the group II metabotropic glutamate receptor agonist, LY354740 on schedule-controlled behavior in rats

AUTHOR(S): Moore, N. A.; Rees, G.; Monn, J. A.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly & Co., Windlesham, Surrey, GU20 6PH, UK

SOURCE: Behavioural Pharmacology (1999), 10(3), 319-325
CODEN: BPHAEL; ISSN: 0955-8810
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study examined the effect of the novel, systemically active Group II metabotropic glutamate (mGlu) receptor agonist, LY354740, on schedule-controlled behavior in rats. Responding for food reward was maintained by three different operant procedures; the first, a three-component conflict schedule; the second, a multiple fixed-interval 60 s/fixed-ratio 10 (FI60/FR10) schedule and the third, a differential reinforcement of low rates of responding 10 s (DRL10) schedule. In the first procedure, rats were trained to respond for food on a schedule comprising of variable-interval 30 s (food, VI30) and fixed-ratio 10 (food + shock, FR10) components separated by time-out (TO). LY354740 (1.25-5 mg/kg, i.p.) produced a dose-related reduction in responding during the VI component and increased responding during the TO component, while having no effect on responding during the punished FR10 phase. In the FI60/FR10 schedule, LY354740 produced a dose-related reduction in the high rates of responding observed during the FR10 component of the schedule. Although LY354740 (0.6-10 mg/kg, i.p.) had no effect on the overall response rates produced by the FI60 component, there was a shift in the temporal distribution of responding as measured by the quarter-life. LY354740 (10 mg/kg, i.p.) increased the low rates towards the start of the interval, while decreasing the rates of responding towards the end of the FI60 period. In the DRL10 s schedule, LY354740 (5-20 mg/kg, i.p.) had no effect on the

total number of responses but produced a significant reduction in the total number of rewards, suggesting that the temporal control of responding had been disrupted. The changes in operant responding occurred at doses that decreased exploratory behavior. In summary, LY354740 modified responding maintained by all three operant schedules at doses which suppressed spontaneous activity. These data demonstrate that stimulation of Group II mGlu receptors can produce changes in responding which are dependent on the base-line rate of responding, suggesting that mGlu 2/3 receptors may be involved in the stimulus and temporal control of behavior.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 116 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:254836 HCAPLUS
DOCUMENT NUMBER: 131:83084
TITLE: Cloning and functional expression of alternative spliced variants of the human metabotropic glutamate receptor 8
AUTHOR(S): Malherbe, Pari; Kratzeisen, Claudia; Lundstrom, Kenneth; Richards, J. Grayson; Faull, Richard L. M.; Mutel, Vincent
CORPORATE SOURCE: Pharma Division PRPN, Preclinical CNS Research, F. Hoffmann-La Roche, Basel, CH-4070, Switz.
SOURCE: Molecular Brain Research (1999), 67(2), 201-210
CODEN: MBREE4; ISSN: 0169-328X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two new spliced variants of the human metabotropic glutamate receptor 8 (HmGluR8), designated HmGluR8b and HmGluR8c, were identified in a human fetal brain cDNA library. The HmGluR8b and c differ from previously reported HmGluR8a by the out-of-frame insertions of 55-bp and 74-bp, resp. The 55-bp insertion which contains a stop codon resulted in substitution of the last 16 amino acids in the C-terminus of HmGluR8a with 16 different amino acids in HmGluR8b. The 74-bp insertion introduces a frame shift in the predicted translation resulting in termination of the polypeptide before the putative seven transmembrane domains. Thus, the predicted HmGluR8c protein is 501 amino acids long and could represent a secreted isoform of the receptor. The pattern of mRNA expression of mGluR8 variants in human brain were analyzed by RT-PCR, Northern blot and in situ hybridization. Both HmGluR8a and b are expressed with similar abundance in fetal and adult brains. The in situ hybridization results indicate a predominantly glial cell expression of HmGluR8c in human brain. The three isoforms were transiently expressed in CHO cells from Semliki Forest Virus vectors. [3H]l-AP4 binding was performed on the cell membranes and the saturation curves showed the presence of a binding site with KD values of 249 and 182 nM and Bmax values of 13.6 and 10.5 pmoles/mg protein for HmGluR8a and b, resp. For the six mGluR ligands studied, a similar rank order of potency was observed on both HmGluRa and b: l-AP4>l-SOP=l-CCG I>l-glutamate>DCG IV>LY 354740.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 117 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:250929 HCAPLUS

DOCUMENT NUMBER: 131:67631
TITLE: Agonist selectivity of mGluR1 and mGluR2 metabotropic receptors: a different environment but similar recognition of an extended glutamate conformation
AUTHOR(S): Jullian, Nathalie; Brabet, Isabelle; Pin, Jean-Philippe; Acher, Francine C.
CORPORATE SOURCE: Parc Club Orsay Universite, Molecular Simulations Inc., Orsay, 91893, Fr.
SOURCE: Journal of Medicinal Chemistry (1999), 42(9), 1546-1555
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To investigate the structural requirements for selective activation or blockade of metabotropic glutamate receptors , a pharmacophore model for group I (mGluR1) and group II (mGluR2) agonists was developed. The Apex-3D program was used with a training set of known active, inactive, and/or selective compds. with a wide structural diversity. The pharmacophore models were then validated by testing a set of addnl. known agonists. Competitive antagonist superpositions were also used in order to define more precisely the topol. of the mGluR1 and mGluR2 agonists' recognition site. Both models account for the activity of most potent compds. and show that the selectivity between mGluR1 and mGluR2 subtypes may be due to excluded vols. and addnl. binding sites, while the relative spatial position of functional groups (NH2, α- and γ-CO2H) remains very similar. On both models glutamate lies in an extended form. An addnl. binding site is disclosed on mGluR1, while this region would be forbidden on mGluR2. This new site combines a closed and an open model for mGluR1 and accounts for the increased affinity of quisqualic acid. The models show another large hydrophobic region which is tolerated for mGluR2 and restricted for mGluR1.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 118 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:193822 HCAPLUS
DOCUMENT NUMBER: 130:242314
TITLE: Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid pharmaceuticals as anxiolytics
INVENTOR(S): Helton, David Reed; Kallman, Mary Jeanne; Monn, James Allen; Schoepp, Darryle Darwin; Tizzano, Joseph Patrick
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: U.S., 8 pp., Cont.-in-part of U.S. Ser. No. 496,710, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5882671	A	19990316	US 1997-786170	19970121
IN 1995CA00927	A	20050701	IN 1995-CA927	19950808
RU 2152925	C1	20000720	RU 1995-113894	19950811

CA 2195782	A1	19960222	CA 1995-2195782	19950814
CN 1123272	A	19960529	CN 1995-115896	19950814
CN 1066135	B	20010523		
ZA 9506773	A	19970214	ZA 1995-6773	19950814
ES 2162936	T3	20020116	ES 1995-930169	19950814
PT 776201	T	20020328	PT 1995-930169	19950814
PRIORITY APPLN. INFO.:			US 1994-289957	B2 19940812
			US 1994-337349	B2 19941110
			US 1995-496710	B2 19950629

AB The present invention provides a method of treating anxiety and related disorders using an agonist, e.g., 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (I) which acts at neg. coupled cAMP-linked metabotropic glutamate receptors. Hard gelatin capsules were prepared from I 250, dried starch 200, and magnesium stearate 10 mg. I was prepared in a series of reactions starting from 1,8-diazabicyclo[5.4.0]undec-7-ene and carbethoxymethyldimethylsulfonium bromide.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 119 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:763175 HCAPLUS
DOCUMENT NUMBER: 130:105594
TITLE: Characterization of (2S,2'R,3'R)-2-(2',3'-[3H]-Dicarboxycyclopropyl)glycine binding in rat brain
AUTHOR(S): Mutel, Vincent; Adam, Geo; Chaboz, Sylvie; Kemp, John A.; Klingelschmidt, Agnes; Messer, Jurg; Wichmann, Jurgen; Woltering, Thomas; Richards, John Grayson
CORPORATE SOURCE: Pharma Division Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Journal of Neurochemistry (1998), 71(6), 2558-2564
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB (2S,2'R,3'R)-2-(2',3'-[3H]Dicarboxycyclopropyl)glycine ([3H]DCG IV) binding was characterized in vitro in rat brain cortex homogenates and rat brain sections. In cortex homogenates, the binding was saturable and the saturation isotherm indicated the presence of a single binding site with a KD value of 180 nM and a Bmax of 780 fmol/mg of protein. The nonspecific binding, measured using 100 μM LY 354740, was <30%. NMDA, AMPA, kainate, L(-)-threo-3-hydroxyaspartic acid, and (S)-3,5-dihydroxyphenylglycine were all inactive in [3H]DCG IV binding up to 1 mM. However, several compds. inhibited [3H]DCG IV binding in a concentration-dependent manner with the following rank order of potency: LY 341495 = LY 354740 > DCG IV = (2S,1'S,2'S)-2-(2-carboxycyclopropyl)glycine > (1S,3R)-1-amino-cyclopentane-1,3-dicarboxylic acid > (2S,1'S,2'S)-2-methyl-2-(2-carboxycyclopropyl)glycine > L-glutamate = ibotenate > quisqualate > (RS)-α-methyl-4-phosphonophenylglycine = L(+)-2-amino-3-phosphonopropionic acid > (S)-α-methyl-4-carboxyphenylglycine > (2S)-α-ethylglutamic acid > L(+)-2-amino-4-phosphonobutyric acid. N-Acetyl-L-aspartyl-L-glutamic acid inhibited the binding in a biphasic manner with an IC50 of 0.2 μM for the high-affinity component. The binding was also affected by GTPγS, reducing agents, and CdCl2. In parasagittal sections of rat brain, a high d. of specific binding was observed in the accessory olfactory bulb, cortical regions (layers 1, 3, and 4 > 2, 5, and 6), caudate

putamen, mol. layers of the hippocampus and dentate gyrus, subiculum, presubiculum, retrosplenial cortex, anteroventral thalamic nuclei, and cerebellar granular layer, reflecting its preferential (perhaps not exclusive) affinity for pre- and postsynaptic metabotropic glutamate mGlu2 receptors. Thus, the pharmacol., tissue distribution, and sensitivity to GTPγS show that [3H]DCG IV binding is probably to group II metabotropic glutamate receptors in rat brain.

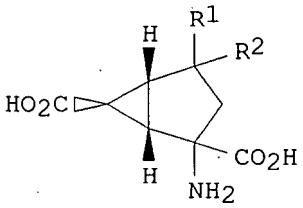
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 120 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:760027 HCAPLUS
DOCUMENT NUMBER: 130:4081
TITLE: Preparation of bicyclic glutamate analogs as excitatory amino acid receptor modulators
INVENTOR(S): Massey, Steven Marc; Monn, James Allen; Valli, Matthew John
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: Eur. Pat. Appl., 35 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 878463	A1	19981118	EP 1998-303730	19980513
EP 878463	B1	20001220		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
ZA 9803930	A	19991108	ZA 1998-3930	19980508
US 5958960	A	19990928	US 1998-78337	19980513
AT 198190	T	20010115	AT 1998-303730	19980513
ES 2152738	T3	20010201	ES 1998-303730	19980513
CA 2289472	A1	19981119	CA 1998-2289472	19980514
CA 2289472	C	20070424		
WO 9851655	A1	19981119	WO 1998-US9862	19980514
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9873869	A	19981208	AU 1998-73869	19980514
AU 729632	B2	20010208		
BR 9808787	A	20000711	BR 1998-8787	19980514
TR 9902777	T2	20000721	TR 1999-2777	19980514
HU 200001404	A2	20000828	HU 2000-1404	19980514
JP 2001525825	T	20011211	JP 1998-549543	19980514
TW 505623	B	20021011	TW 1998-87107483	19980514
CN 1125807	B	20031029	CN 1998-804992	19980514
US 6160009	A	20001212	US 1999-322651	19990528
NO 9905480	A	19991109	NO 1999-5480	19991109
MX 9910380	A	20000430	MX 1999-10380	19991111

US 6268507	B1	20010731	US 2000-637143	20000811
GR 3035156	T3	20010430	GR 2000-402844	20001227
PRIORITY APPLN. INFO.:			US 1997-47011P	P 19970514
			US 1998-78337	A3 19980513
			WO 1998-US9862	W 19980514
			US 1999-322651	A3 19990528

OTHER SOURCE(S): MARPAT 130:4081
GI



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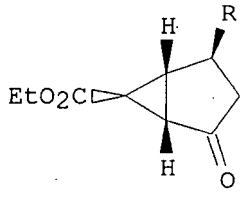
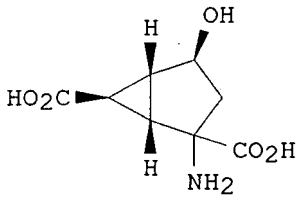


II



III

AB Bicyclic glutamate analogs I [R1 = F, XOR3, XNR4R5, SO3H, 5-tetrazolyl, CN, PO3R62, N3, (CH2)mCOR3a, (CH2)mPO3R6a2, NHCONHR3b, NHSO2R3c, R2 = H; R1 = R2 = F; R1R2 = O, NOR7, CR8R9, CHCO2R3b, CHPO3R6a2, CHCN; one of R1 and R2 = amino, and the other = carboxyl; R3, R3a, R3b, R3c, R5, R7, R8, R9, R10 = H, (un)substituted C1-6 alkyl, C3-6 alkenyl, C3-6 alkynyl, aryl, heteroaryl, (un)fused carbocyclyl, (un)fused heterocyclyl; X = CH2, CO; m = 1-3; R4 = COR10, any group R3; R6, R6a = H, C1-6 alkyl], and non-toxic metabolically labile ester and amides thereof, and pharmaceutically acceptable salts thereof, are prepared as modulators of metabotropic glutamate receptor function. Thus, cyclopropanation of 2-cyclopenten-1-one with (carbethoxymethyl)dimethylsulfonium bromide (preparation given) gave 68% bicyclic ester II (R = H). II (R = H) was converted into hydroxy derivative II (R = OH) via silyl enol ether formation, oxidation to the corresponding α,β-unsatd. ketone, epoxidn., and ring opening. Cyclocondensation of II (R = OH) with KCN and ammonium formate gave the corresponding spirohydantoin, which was hydrolyzed with aqueous NaOH to give bicyclic amino acid III.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 121 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:660994 HCAPLUS
DOCUMENT NUMBER: 130:32948
TITLE: Effects of the selective metabotropic glutamate agonist LY354740 in a rat model of permanent ischemia

AUTHOR(S): Lam, Amy G. M.; Soriano, Marc A.; Monn, James A.; Schoepp, Darryle D.; Lodge, David; McCulloch, James
CORPORATE SOURCE: Wellcome Surgical Institute and Hugh Fraser Neuroscience Laboratories, University of Glasgow, Glasgow, G61 1QH, UK
SOURCE: Neuroscience Letters (1998), 254(2), 121-123
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuroprotective effects of a systemically active, potent, group II selective metabotropic glutamate receptor agonist, LY354740, was assessed in the middle cerebral artery occlusion model of focal ischemia in rats. LY354740 (0.3, 3.0 or 30.0 mg/kg) was administered s.c. 30 min prior to and 3 h after the induction of ischemia. Twenty four hours after the ischemic insult, the brains were processed for the evaluation of infarct vols. No significant reduction in infarct vols. were observed in treated animals at any of the doses investigated. These data provide no support for the view that group II metabotropic glutamate receptors have a major influence on ischemic damage in this model.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 122 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:627116 HCAPLUS
DOCUMENT NUMBER: 130:148522
TITLE: LY354740, a group II metabotropic glutamate receptor agonist with potential antiparkinsonian properties in rats
AUTHOR(S): Konieczny, J.; Ossowska, K.; Wolfarth, S.; Pilc, A.
CORPORATE SOURCE: Institute of Pharmacology, Department of Neuro-Psychopharmacology, Polish Academy of Sciences, Krakow, PL-31-343, Pol.
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1998), 358(4), 500-502
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to examine whether (+)-2-aminobicyclo[3.1.0]-hexane-2,6-dicarboxylate monohydrate (LY354740), a selective agonist of group II metabotropic glutamate receptors, possesses antiparkinsonian properties. Parkinsonian-like muscle rigidity was induced by pretreatment with haloperidol (1 mg/kg i.p.). It was measured as increased resistance developed by the rat's hind leg to passive extension and flexion. LY354740 (5 and 10 mg/kg i.p.) dose-dependently diminished the haloperidol-induced muscle rigidity. The present results suggest that LY354740 counteracts the muscle rigidity in an animal model of parkinsonism.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 123 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:611270 HCAPLUS
DOCUMENT NUMBER: 130:720
TITLE: Presynaptic inhibitory action of the group II

metabotropic glutamate receptor agonists, LY354740 and DCG-IV

AUTHOR(S): Kilbride, John; Huang, LingQian; Rowan, Michael J.; Anwyl, Roger

CORPORATE SOURCE: Department of Physiology, Trinity College, Dublin, Ire.

SOURCE: European Journal of Pharmacology (1998), 356(2/3), 149-157
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Electrophysiol. studies were carried out on the presynaptic inhibitory action of the group II metabotropic glutamate (mGlu) receptor agonists (+)-2-aminobicyclo[3.1.0]hexane-2-6-dicarboxylic acid (LY354740) and (2S,1'R,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine (DCG-IV) in three paths of the rat hippocampus, the medial and lateral perforant path to the dentate gyrus, and the Schaffer collateral/commissural path to CA1. LY354740 caused a dose-dependent reversible inhibition of the field excitatory postsynaptic potential (EPSP) in the medial and lateral perforant paths, with an EC50 of 115 nM and 230 nM, resp. Maximal inhibition by LY354740 was much greater in the medial path (about 80%) than in the lateral path (about 50%). No inhibition was observed in CA1. A presynaptic inhibition was confirmed by LY354740 inducing dose-dependent changes in paired-pulse depression/facilitation. DCG-IV had a similar action to LY354740, but with a lower potency.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 124 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:527203 HCAPLUS

DOCUMENT NUMBER: 129:156945

TITLE: Treatment for premenstrual dysphoric disorder

INVENTOR(S): Levine, Louise R.

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832436	A1	19980730	WO 1998-US1344	19980123
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2275777	A1	19980730	CA 1998-2275777	19980123
AU 9862487	A	19980818	AU 1998-62487	19980123
EP 1014971	A1	20000705	EP 1998-904669	19980123
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				

JP 2001511131	T	20010807	JP 1998-532158		19980123
PRIORITY APPLN. INFO.:			US 1997-36176P	P	19970129
			WO 1998-US1344	W	19980123

AB Agonists which act at neg.-coupled cAMP-linked metabotropic glutamate receptors are useful for treating premenstrual dysphoric disorder. An example compound which was synthesized is 1SR,4SR,5SR,6SR-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 125 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:490373 HCAPLUS
DOCUMENT NUMBER: 130:119421
TITLE: Potent, stereoselective, and brain region selective modulation of second messengers in the rat brain by (+)LY354740, a novel group II metabotropic glutamate receptor agonist
AUTHOR(S): Schoepp, D. D.; Johnson, Bryan G.; Wright, Rebecca A.; Salhoff, Craig R.; Monn, James A.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1998), 358(2), 175-180
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY354740 is a highly potent and selective agonist for recombinant Group II mGlu receptors (mGlu2 and mGlu3), which has anxiolytic and drug withdrawal alleviating properties when administered systemically in rats and mice. The modulation of second messengers by LY354740 in rat brain tissues was investigated to understand the cellular basis for the pharmacol. and potential therapeutic actions of LY354740. LY354740 potently decreased forskolin-stimulated cAMP formation in slices of the adult rat hippocampus (EC50=22±3 nM) in a stereoselective manner. LY354740 (at 1 μM) greatly (>90%) suppressed forskolin-stimulated cAMP in the cerebral cortex, hippocampus, and striatum, while producing only partial suppression (about 50%) in midbrain regions and olfactory bulb, and no significant cAMP alterations in the cerebellum and brainstem regions. Inhibition of forskolin-stimulated cAMP formation was antagonized by (+)-α-methyl-4-carboxyphenylglycine [(+)MCPG], a competitive mGlu receptor antagonist. LY354740 did not alter phosphoinositide hydrolysis in the rat hippocampus per se, but potentiated stimulation of phosphoinositide hydrolysis by the Group I mGlu receptor selective agonist 3,5-dihydroxyphenylglycine (DHPG) or stimulation of cAMP formation by the adenosine receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA). These data indicate that LY354740 is a highly potent, efficacious, and selective Group II mGlu receptor (mGlu 2/3) agonist in the rat brain. The potent, stereoselective, and brain region selective actions of LY354740 on mGlu receptor linked second messenger systems likely underlie the in vivo potency and stereoselectivity of this compound in animal models.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 126 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:376205 HCAPLUS
DOCUMENT NUMBER: 129:156782

TITLE: A role for metabotropic glutamate receptors in drug withdrawal states
AUTHOR(S): Helton, David R.; Schoepp, Darryle D.; Monn, James A.; Tizzano, Joseph P.; Kallman, Mary Jeanne
CORPORATE SOURCE: CNS Behavioral Laboratory, Lilly Research Laboratories, Eli Lilly and, Greenfield, IN, 46140, USA
SOURCE: Portland Press Proceedings (1998), 12(Metabotropic Glutamate Receptors and Brain Function), 305-314
CODEN: POPPEF; ISSN: 0966-4068
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to further examine the role of metabotropic glutamate receptors function in nicotine and benzodiasepine withdrawal, the authors examined the effects of LY314582 on sensorimotor responsiveness following cessation of chronic exposure to nicotine or the benzodiasepine, diazepam.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 127 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:331366 HCAPLUS
DOCUMENT NUMBER: 129:16393
TITLE: Preparation of bicyclic excitatory amino acids
INVENTOR(S): Monn, James A.; Schoepp, Darryle D.
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: U.S., 16 pp., Cont.-in-part of U.S. Ser. No. 337,349, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5750566	A	19980512	US 1995-496643	19950629
IN 1995CA00927	A	20050701	IN 1995-CA927	19950808
PL 182285	B1	20011231	PL 1995-309972	19950810
EP 696577	A1	19960214	EP 1995-305632	19950811
EP 696577	B1	19981014		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
HU 75524	A2	19970528	HU 1995-2380	19950811
HU 223845	B1	20050228		
AT 172186	T	19981015	AT 1995-305632	19950811
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IL 114910	A	20000629	IL 1995-114910	19950811
RU 2152925	C1	20000720	RU 1995-113894	19950811
IL 133493	A	20020210	IL 1995-133493	19950811
CA 2156024	A1	19960213	CA 1995-2156024	19950814
CA 2156024	C	20041005		
FI 9503837	A	19960213	FI 1995-3837	19950814
FI 114861	B1	20050114		
NO 9503191	A	19960213	NO 1995-3191	19950814
AU 9528530	A	19960222	AU 1995-28530	19950814
AU 692276	B2	19980604		

WO 9605175		A1	19960222	WO 1995-US10319	19950814
W:	AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
RW:	KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9533251		A	19960307	AU 1995-33251	19950814
BR 9503638		A	19960528	BR 1995-3638	19950814
CN 1123272		A	19960529	CN 1995-115896	19950814
CN 1066135		B	20010523		
JP 08188561		A	19960723	JP 1995-207010	19950814
JP 2883297		B2	19990419		
ZA 9506773		A	19970214	ZA 1995-6773	19950814
SK 281288		B6	20010212	SK 1997-133	19950814
CZ 291270		B6	20030115	CZ 1995-2074	19950814
RO 119147		B1	20040430	RO 1997-275	19950814
TW 438741		B	20010607	TW 1995-84108531	19950816
US 5925782		A	19990720	US 1997-851154	19970505
US 5925680		A	19990720	US 1997-935737	19970923
HK 1013983		A1	20000714	HK 1998-115178	19981223
CZ 291663		B6	20030416	CZ 2002-2544	20020722
PRIORITY APPLN. INFO.:				US 1994-289957	B2 19940812
				US 1994-337349	B2 19941110
				US 1995-496643	A 19950629
				IL 1995-114910	A3 19950811
				CZ 1995-2074	A3 19950814
				WO 1995-US10319	W 19950814

OTHER SOURCE(S): MARPAT 129:16393

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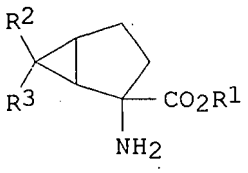

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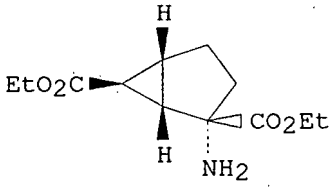

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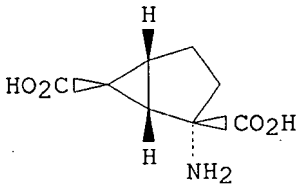
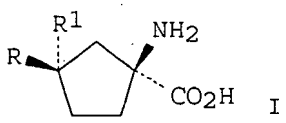


III

AB The present invention provides novel bicyclic amino acids I (R2 = CO2R4, R3 = H; R2 = H, R3 = CO2R4; R1, R4 = independently H, C1-10 alkyl, C2-20 alkenyl, aryl, arylalkyl) or pharmaceutically acceptable salts thereof, that affect certain excitatory amino acid receptors, especially neg.-coupled

L9 ANSWER 128 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:312737 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 129:90313
TITLE: Neuroprotective effects of a systemically active group II metabotropic glutamate receptor agonist LY354740 in a gerbil model of global ischemia
AUTHOR(S): Bond, Ann; O'neill, Michael J.; Hicks, Caroline A.; Monn, James A.; Lodge, David
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Co, Erl Wood Manor, Surrey, GU20 6PH, UK
SOURCE: NeuroReport (1998), 9(6), 1191-1193
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The neuroprotective effects of a novel Group II metabotropic glutamate receptor (mGluR) agonist, LY354740, have been evaluated in a gerbil model of global ischemia. When administered at 50 mg/kg, i.p., 30 min and 6 h after a 3 min period of bilateral carotid artery occlusion (BCAO), the compound reduced the damage to CA1 hippocampal neurons to a significant level. However, when the ischemic insult was made more severe, by increasing the period of occlusion to 4 and 5 min, the neuroprotective effects of LY354740 were reduced. From these findings, it would appear that Group II mGluRs may play a role in ischemic damage in the gerbil hippocampus and that agonists at these receptors are potential neuroprotective agents.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 129 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:270298 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 129:67520
TITLE: Synthesis and Biology of the Conformationally Restricted ACPD Analog, 2-Aminobicyclo[2.1.1]hexane-2,5-dicarboxylic Acid-I, a Potent mGluR Agonist
AUTHOR(S): Kozikowski, Alan P.; Steensma, Darryl; Araldi, Gian Luca; Tueckmantel, Werner; Wang, Shaomeng; Pshenichkin, Sergey; Surina, Elena; Wroblewski, Jarda
CORPORATE SOURCE: Drug Discovery Program Institute of Cognitive and Computational Sciences, Georgetown University Medical Center, Washington, DC, 20007-2197, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(10), 1641-1650
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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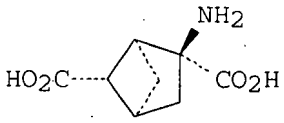

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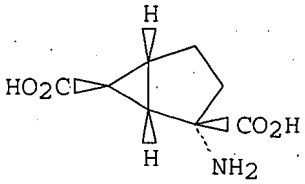
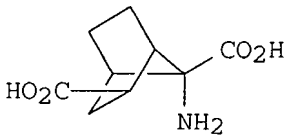


III



IV

AB To better characterize the roles of metabotropic glutamate receptors (mGluRs) in physiol. and pathophysiol. processes, there is an important need to learn more about the structural features relevant to the design of novel, high-affinity ligands that are family and subtype specific. To date, many of the biol. studies that have been conducted in the area of mGluR research have made use of the cyclopentanedicarboxylic acid agonist (1S,3R)-ACPD I (R = CO2H, R1 = H). I has been shown to act as an agonist at both the group I and group II receptors while showing little selectivity among the four subtypes belonging to these two groups. Moreover, (1S,3S)-ACPD I (R = H, R1 = CO2H), the cis isomer, shows negligible activity at group I receptors and is a good agonist of mGluR2. Since I (R, R1 = H, CO2H) is itself somewhat flexible, with four distinctive conformations being identified from mol. modeling studies for the trans isomer and five conformations for the cis isomer, we believed that it would be of interest to examine the activity of an ACPD analog that has been constrained through the introduction of a single carbon atom bridge. Accordingly, we have prepared an aminobicyclo[2.1.1]hexanedicarboxylic acid (ABHxD-I) II as an analog of I. The synthesis of this compound was accomplished by use of an intramol. [2 + 2] photocycloaddn. reaction, in which four distinct diastereomers were isolated. Of these four compds., only a single isomer II was found to be a potent agonist of the mGluRs. II, which expresses the fully extended glutamate conformation, was found to be more potent than I at all six of the eight mGluR subtypes that were investigated and to be comparable to or more potent than the endogenous ligand, glutamate, for these receptors. Interestingly, despite its fixed conformation, I, like glutamate, shows little subtype selectivity. Through modeling studies of II, aminonorbornanedicarboxylic acid III (ABHD-VI), aminobicyclohexanedicarboxylic acid IV (LY354740), I (R = CO2H, R1 = H), I (R = H, R1 = CO2H), and L-glutamate, we conclude that the aa conformation of L-glutamate is the active conformation for both group I and group II mGluRs. Moreover, the modeling-based comparisons of these ligands suggest that the selectivity exhibited by LY354740 between the group I and group II mGluRs is not a consequence of different conformations of L-glutamate being required for recognition at these mGluRs but rather is related to certain structural elements within certain regions having a very different impact on the group I and group II mGluR activity. The enhanced potency of ABHxD-I relative to trans-ACPD commends it as a useful starting point in the design of subtype selective mGluR ligands.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 130 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:154394 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 128:266076
TITLE: LY354740: a metabotropic glutamate receptor agonist which ameliorates symptoms of nicotine withdrawal in rats
AUTHOR(S): Helton, D. R.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D.; Kallman, M. J.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Greenfield, IN, 46140, USA
SOURCE: Neuropharmacology (1998), Volume Date 1997, 36(11/12), 1511-1516
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LY354740 is a conformationally constrained analog of glutamate with high selectivity and nanomolar agonist activity at Group II metabotropic glutamate receptors (mGluRs). This orally active compound is a new drug candidate which is being developed for the treatment of anxiety. In this study, LY354740 was investigated in a model of nicotine withdrawal using the acoustic startle reflex (sensorimotor reactivity) in rats. Nicotine (6 mg/kg/day) was administered for 12 days s.c. by osmotic minipumps. After 12 days the pumps were removed and the animals were allowed to go through spontaneous withdrawal. Cessation of chronic nicotine exposure led to increased startle responding for 4 days following withdrawal. Treatment with LY354740 (0.0001-0.1 mg/kg, i.p.; 0.03-3 mg/kg, oral) produced a dose-dependent attenuation of the enhanced auditory startle responding following withdrawal of nicotine with i.p. and oral ED50 values of 0.003 mg/kg and 0.7 mg/kg, resp. These effects were stereoselective since the (-)-enantiomer of LY354740, LY366563, was without effect in this model. LY354740 produced no changes in the sensorimotor reactivity of rats not exposed to nicotine at oral doses up to 10 mg/kg. These data support the functional role of mGluR agonists in nicotine withdrawal and indicate that LY354740 may be efficacious in reducing the symptoms associated with nicotine withdrawal during smoking cessation in humans.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 131 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:129246 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 128:254667
TITLE: In vitro binding characteristics of a new selective group II metabotropic glutamate receptor radioligand, [3H]LY354740, in rat brain
AUTHOR(S): Schaffhauser, Herve; Richards, J. Grayson; Cartmell, Jayne; Chaboz, Sylvie; Kemp, John A.; Klingelschmidt, Agnes; Messer, Jurg; Stadler, Heinz; Woltering, Thomas; Mutel, Vincent
CORPORATE SOURCE: Pharma Division Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Molecular Pharmacology (1998), 53(2), 228-233
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The in vitro binding of [3H]LY354740, the first high affinity group II-selective metabotropic glutamate (mGlu) receptor radioligand, was characterized in rat cortical, hippocampal, and thalamic membranes as well as in rat brain sections. [3H]LY354740 binding was saturable in all regions investigated. Nonspecific binding (in the presence of 10 μM DCG-IV) was ≈8% of the total. Ionotropic glutamate receptor agonists, N-methyl-D-aspartate, (R,S)-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate, a Na+-dependent glutamate uptake blocker as well as a group I-selective mGlu receptor agonist (all up to 1 mM) did not inhibit [3H]LY354740 binding to cortical membranes. However, several known metabotropic receptor ligands inhibited the binding with the following rank order of potency: LY354740 = LY341495 > (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine = (2S,1',S,2'S)-2-(2-carboxycyclopropyl)glycine > glutamate = (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid > (2S,1'S,2'S)-2-methyl-2-(2-carboxycyclopropyl)glycine > quisqualate > ibotenate > L-2-amino-3-phosphonopropionic acid = (S)-α-methyl-4-carboxyphenylglycine > L-(+)-2-amino-4-phosphonobutyric acid. N-Acetyl-aspartyl-glutamate, (2S)-α-ethylglutamic acid, and (R,S)-α-methyl-4-phosphonophenylglycine inhibited [3H]LY354740 binding in a biphasic manner. Guanosine-5'-O-(3-thiotriphosphate) concentration-dependently and almost completely inhibited the binding. Finally, in parasagittal sections of rat brain, a high d. of specific binding was observed in the accessory olfactory bulb, cortical regions (layers 1-3>4-6), caudate putamen, mol. layers of the hippocampus and dentate gyrus, presubiculum, retrosplenial cortex, anteroventral thalamic nuclei, and cerebellar granular layer, reflecting its preferential (perhaps not exclusive) affinity for presynaptic and postsynaptic mGlu2 receptors. Thus, the pharmacol., tissue distribution, and sensitivity to guanosine-5'-O-(3-thiotriphosphate) show that [3H]LY354740 binding probably occurs to group II mGlu receptors in rat brain.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 132 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:111752 HCAPLUS <<LOGINID::20070726>>

DOCUMENT NUMBER: 128:239324

TITLE: Anxiolytic and side-effect profile of LY354740: a potent, highly selective, orally active agonist for group II metabotropic glutamate receptors

AUTHOR(S): Helton, David R.; Tizzano, Joseph P.; Monn, James A.; Schoepp, Darryle D.; Kallman, Mary Jeanne

CORPORATE SOURCE: Toxicology Research, Division, Eli Lilly and Company, Greenfield, IN, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 284(2), 651-660
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB LY354740 is a conformationally constrained analog of glutamate which is a potent agonist for group II cAMP coupled metabotropic glutamate receptors (mGluRs). The discovery of this novel pharmacol. agent has allowed the exploration of the functional consequences of activating group II mGluRs in vivo. In an effort to evaluate the clin. utility of LY354740 as an anxiolytic, we examined its

effects in the fear potentiated startle and elevated plus maze models of anxiety and compared the results with the clin. prescribed anxiolytic diazepam. In the fear potentiated startle and elevated plus maze models, both LY354740 and diazepam produced significant anxiolytic activity (ED50 values of 0.3 and 0.4 mg/kg p.o. for fear potentiated startle and 0.2 and 0.5 mg/kg for the elevated plus maze, resp.). The duration of pharmacol. effect for LY354740 in the efficacy models was 4 to 8 h. In contrast to diazepam, acute administration of LY354740 did not produce sedation, cause deficits in neuromuscular coordination, interact with central nervous system depressants, produce memory impairment or change convulsive thresholds at doses 100- to 1000-fold the efficacious doses in animal models of anxiety. Thus, LY354740 has anxiolytic activity in animal models that are sensitive to benzodiazepines such as diazepam. However, at anxiolytic doses in these models, LY354740 produced none of the unwanted secondary pharmacol. associated with diazepam. These data indicate a functional role for group II mGluRs in fear/anxiety responses in animals and suggest that compds. in this class may be beneficial in the treatment of anxiety-related disorders in humans without the side effects seen with currently prescribed medications.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 133 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:45182 HCAPLUS <<LOGINID::20070726>>

DOCUMENT NUMBER: 128:123439

TITLE: Substituted (2SR)-2-((1SR,2SR)-2-carboxycycloprop-1-yl)glycines as Potent and Selective Antagonists of Group II Metabotropic Glutamate Receptors. 2. Effects of Aromatic Substitution; Pharmacological Characterization, and Bioavailability

AUTHOR(S): Ornstein, Paul L.; Bleisch, Thomas J.; Arnold, M. Brian; Wright, Rebecca A.; Johnson, Bryan G.; Tizzano, Joseph P.; Helton, David R.; Kallman, Mary Jeanne; Schoepp, Darryle D.; Herin, Marc

CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company Lilly Corporate Center, Indianapolis Indiana 46285, IN, 46285, USA

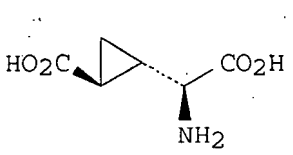
SOURCE: Journal of Medicinal Chemistry (1998), 41(3), 358-378
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



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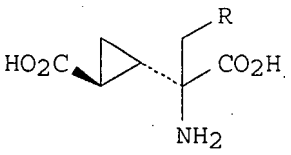

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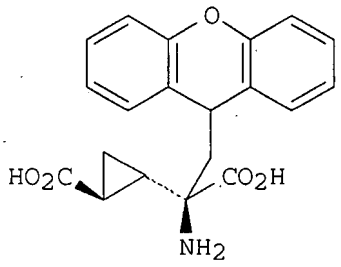


II

AB In this paper the authors describe the synthesis of a series of α-substituted analogs of the potent and selective group II metabotropic glutamate receptor (mGluR) agonist (1S,1'S,2'S)-carboxycyclopropylglycine (I). Incorporation of a substituent on the amino acid carbon converted the agonist I into an antagonist. All of the compds. were prepared and tested as a series of four isomers, i.e., two racemic diastereomers. On the basis of the improvement in affinity realized for the α-phenylethyl analog II (R = CH2Ph), in this paper the authors explored the effects of substitution on the aromatic ring as a strategy to increase the affinity of these compds. for group II mGluRs. Affinity for group II mGluRs was measured using [3H]glutamic acid (Glu) binding in rat forebrain membranes. Antagonist activity was confirmed for these compds. by measuring their ability to antagonize (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid-induced inhibition of forskolin stimulated cyclic-AMP in RGT cells transfected with human mGluR2 and mGluR3. Meta substitution on the aromatic ring of II (R = CH2Ph) with a variety of substituents, both electron donating (R = 3-R1C6H4CH2; R1 = 3-Me, 3-OH, 3-NH2, 3-OMe, 3-Ph, 3-PhO) and electron withdrawing (R1 = 3-F, 3-Cl, 3-Br, 3-CO2H, 3-CF3) gave from 1.5- to 4.5-fold increases in affinity. Substitution with p-F (II; R = 4-FC6H4CH2) (IC50 = 0.022 ± 0.002), was the exception. Here, a greater increase in affinity was realized than for either the ortho- or meta-substituted analogs; II (R = 4-FC6H4CH2) was the most potent compound resulting from monosubstitution of the aromatic At best, only modest increases in affinity were realized for certain compds. bearing either two chlorines or two fluorines, and two methoxy groups gave no improvement in affinity (all examined in a variety of substitution patterns). Three amino acids II (R1 = CHPh2, 9-xanthyl, 3-MeC6H4CH2) were resolved into their four constituent isomers, and affinity and functional activity for group II mGluRs was found to reside solely in the S,S,S-isomers of each, consistent with I. With an IC50 = 2.9 ± 0.6 nM, the resolved xanthylmethyl compound (S,S,S)-III (LY341495) was the most potent compound from this SAR. (S,S,S)-III demonstrated high plasma levels following i.p. (i.p.) administration and readily penetrated into the brain. This compound, however, had only limited (.apprx.5%) oral bioavailability. Systemic administration of (S,S,S)-III protected mice from limbic seizures produced by the mGluR agonist 3,5-dihydroxyphenylglycine, with an ED50 = 31 mg/kg (i.p., 60 min

preinjection). Thus, (S,S,S)-III represents a valuable tool to study the role of group II mGluRs in disease.

L9 ANSWER 134 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:573924 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 127:257889
TITLE: Involvement of a cyclic-AMP pathway in group I metabotropic glutamate receptor responses in neonatal rat cortex
AUTHOR(S): Schaffhauser, Herve; de Barry, Jean; Muller, Helene; Heitz, Marie-Paule; Gombos, Georges; Mutel, Vincent
CORPORATE SOURCE: Pharma Division Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: European Journal of Pharmacology (1997), 334(2/3), 289-297
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 3,5-Dihydroxyphenylglycine (DHPG), (S)-3-hydroxyphenylglycine and (S)-4-carboxy-3-hydroxyphenylglycine (S-4C3HPG) stimulated phosphoinositide hydrolysis in neonatal rat cortical slices, but with lower maximal effect, in comparison with 2S,1'S,2'S-2-(2'-carboxycyclopropyl)glycine (L-CCG I) or (1S,3R)-1-aminocyclo-pentane-1,3-dicarboxylic acid (1S,3R-ACPD). DHPG, 1S,3R-ACPD, and S-4C3HPG also evoked a rapidly desensitizing increase in [Ca2+]i in cortical layers of neonatal brain slices. (R,S)-α-methyl-4-tetrazolylphenylglycine (MTPG), and (R,S)-α-methyl-4-phosphono-phenylglycine (MPPG) inhibited the increase of phosphoinositide hydrolysis elicited by 1S,3R-ACPD but not that by R,S-DHPG. In contrast, the selective group II receptor agonist (1S,2S,5R,6S)-2-amino-bicyclo-[3.1.0]-hexane-2,6-dicarboxylate (LY 354740) potentiated the response of R,S-DHPG. Finally, 8-(4-chlorophenylthio)-cAMP, a membrane permeant analog of cAMP, reversed the stimulatory effect of 1S,3R-ACPD and S-4C3HPG on phosphoinositide hydrolysis and [Ca2+]i mobilization, without affecting the response induced by R,S-DHPG. These data suggest that, in neonatal rat cortex, the activation of group II metabotropic glutamate receptors potentiates the phosphoinositide hydrolysis and [Ca2+]i responses mediated by group I metabotropic glutamate receptors.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 135 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:494642 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 127:157062
TITLE: Pharmacological characterization of metabotropic glutamate receptors linked to the inhibition of adenylate cyclase activity in rat striatal slices
AUTHOR(S): Schaffhauser, H.; Cartmell, J.; Jakob-Rotne, R.; Mutel, V.
CORPORATE SOURCE: PRPN 70/325, Pharma Division Preclinical CNS Research, F. Hoffmann-La Roche Ltd, Basel, CH 4070, Switz.
SOURCE: Neuropharmacology (1997), 36(7), 933-940
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacol. profile of mGlu receptors neg. linked to adenylyl cyclase was characterized in adult rat striatal slices. Among the mGlu agonists tested, LY 354740, was the most potent inhibitor of forskolin-stimulated cAMP formation (EC50 = 11 nM). Inhibition of forskolin stimulation by the group III agonist L-2-amino-4-phosphonobutanoate (L-AP4) was biphasic, the two parts of the concentration curve having EC50 values of 6 μM and 260 μM, suggesting a sequential recruitment of mGlu4/8 and mGlu7. The effects of several new phenylglycine derivative antagonists were tested on the inhibition of forskolin cAMP response by (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine (L-CCG I) and L-AP4. At 500 μM, (RS)-α-methyl-3-carboxy-methyl-phenyl-glycine was unable to antagonize the effect of L-CCG I or L-AP4 but (S)-α-methyl-3-carboxy-phenylalanine inhibited the effect of L-AP4 with a low potency. Finally, (RS)-α-methyl-4-tetrazolylphenylglycine and particularly (RS)-α-methyl-4-phosphonophenylglycine, appeared to be the most potent and selective antagonists of L-AP4 induced inhibition of forskolin-stimulated cAMP production in adult rat striatal slices.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 136 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:492449 HCAPLUS <<LOGINID::20070726>>

DOCUMENT NUMBER: 127:117332

TITLE: In vivo inhibition of veratridine-evoked release of striatal excitatory amino acids by the group II metabotropic glutamate receptor agonist LY354740

AUTHOR(S): Battaglia, Giuseppe; Monn, James A.; Schoepp, Darryle D.

CORPORATE SOURCE: Lilly Res. Lab., Lilly Corporate Center, Eli Lilly Co., Indianapolis, IN, 46285, USA

SOURCE: Neuroscience Letters (1997), 229(3), 161-164
CODEN: NELED5; ISSN: 0304-3940

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In vivo microdialysis in freely moving rats was used to investigate the presynaptic mechanisms by which LY354740, a novel, potent, selective, and systemically active agonist for group II metabotropic glutamate receptors (mGluRs), alters glutamate neuronal transmission. Basal levels of glutamate and aspartate in striatal dialyzates of LY354740 (10 mg/kg, i.p.)-treated animal were not different from those in saline-treated control animals. In the controls, veratridine (100 μM) induced a 6-fold increase in glutamate and a 9-fold increase in aspartate. However, following LY354740 administration the veratridine-evoked release of glutamate and aspartate was completely prevented. These data demonstrate that LY354740 blocks the evoked released of endogeneous excitatory amino acids, and indicate a role for group II mGluRs in presynaptic modulation of glutamate neuronal transmission in vivo.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 137 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:440130 HCAPLUS <<LOGINID::20070726>>

DOCUMENT NUMBER: 127:66215

TITLE: Preparation of excitatory amino acid receptor

antagonists

INVENTOR(S): Dominguez-Fernandez, Carmen; Monn, James Allen; Valli, Matthew John

PATENT ASSIGNEE(S): Lilly, Eli and Co., USA

SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW

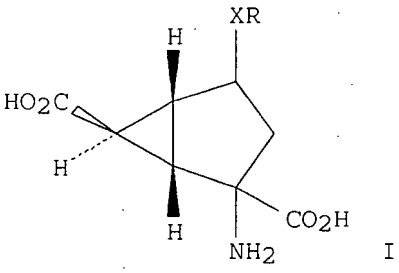
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 774454	A1	19970521	EP 1996-308214		19961114
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
CA 2237404	A1	19970522	CA 1996-2237404		19961112
WO 9717952	A1	19970522	WO 1996-US18577		19961112
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9710784	A	19970605	AU 1997-10784		19961112
AU 703094	B2	19990318			
CN 1207678	A	19990210	CN 1996-198395		19961112
BR 9611509	A	19990302	BR 1996-11509		19961112
JP 2000500754	T	20000125	JP 1997-519158		19961112
US 5912248	A	19990615	US 1996-749304		19961114
PRIORITY APPLN. INFO.:			US 1995-6824P	P	19951116
			GB 1996-5429	A	19960315
			WO 1996-US18577	W	19961112

OTHER SOURCE(S): MARPAT 127:66215

GI



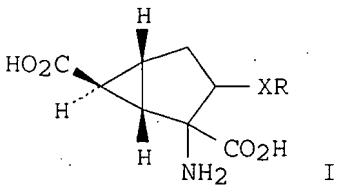
I

AB Aminobicyclohexanedicarboxylic acids I [X = bond, S, SO, SO2; R = (un)substituted alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl] were prepared for use as modulators of metabotropic glutamate receptor function. Thus, 1SR,2RS,4SR,5SR,6SR-2-amino-4-(phenylthio)bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was prepared in several steps starting from carboethoxymethyl dimethylsulfonium bromide, 2-cyclopenten-1-one, and thiophenol. Formulations containing I are described.

L9 ANSWER 138 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:440129 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 127:66214
TITLE: Preparation of excitatory amino acid receptor antagonists
INVENTOR(S): Dominguez-Fernandez, Carmen; Helton, David Reed; Massey, Steven Marc; Monn, James Allen
PATENT ASSIGNEE(S): Lilly, Eli and Co., USA
SOURCE: Eur. Pat. Appl., 45 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 774455	A1	19970521	EP 1996-308215	19961114
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CA 2237598	A1	19970522	CA 1996-2237598	19961112
WO 9717950	A1	19970522	WO 1996-US18207	19961112
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9677310	A	19970605	AU 1996-77310	19961112
AU 703093	B2	19990318		
ZA 9609485	A	19980512	ZA 1996-9485	19961112
CN 1202103	A	19981216	CN 1996-198264	19961112
BR 9611521	A	19990629	BR 1996-11521	19961112
JP 2000500752	T	20000125	JP 1997-519044	19961112
IN 1996CA01960	A	20050304	IN 1996-CA1960	19961112
TW 427973	B	20010401	TW 1996-85113882	19961113
US 5916920	A	19990629	US 1996-749301	19961114
PRIORITY APPLN. INFO.:			US 1995-6871P P	19951116
			GB 1996-5430 A	19960315
			WO 1996-US18207 W	19961112

OTHER SOURCE(S): MARPAT 127:66214
GI



I

X = S

AB Aminobicyclohexanedicarboxylic acids I [X = S, O, NH, NR, NCOR; R = (un)substituted alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl] were prepared for use as modulators of metabotropic glutamate receptor function. Thus, a mixture of

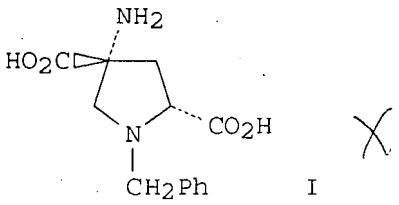
1SR,2SR,3RS,5RS,6SR- and 1SR,2RS,3RS,5RS,6SR-2-amino-3-(phenylpropyl)bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was prepared was prepared in several steps starting from carboethoxymethyl dimethylsulfonium bromide, 2-cyclopenten-1-one, and hydrocinnamaldehyde. Formulations containing I are described.

L9 ANSWER 139 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:387282 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 127:76517
TITLE: A novel orally active Group 2 metabotropic glutamate receptor agonist: LY354740
AUTHOR(S): Bond, Ann; Monn, James A.; Lodge, David
CORPORATE SOURCE: Lilly Research Centre, Erl Wood Manor, Surrey, GU20 6PH, UK
SOURCE: NeuroReport (1997), 8(6), 1463-1466
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nonspecific metabotropic glutamate receptor (mGluR) agonists have previously been shown to potentiate responses of spinal neurons to ionotropic glutamate receptor agonists. In this study we show that LY354740, which is a highly selective Group 2 mGluR agonist with nanomolar potency in vitro, also mimics the above effects following local ejection on spinal neurons in vivo, an action which is blocked by a Group 2 antagonist. Despite its polar nature, LY354740 is also active given either by the i.v. or the oral route (2.5-20 mg/kg) and thus will be a useful agent for investigating the role of Group 2 mGluRs both physiol. and clin.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 140 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:199510 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 126:288381
TITLE: LY354740 is a potent and highly selective group II metabotropic glutamate receptor agonist in cells expressing human glutamate receptors
AUTHOR(S): Schoepp, D. D.; Johnson, B. G.; Wright, R. A.; Salhoff, C. R.; Mayne, N. G.; Wu, S.; Cockerham, S. L.; Burnett, J. Paul; Belegaje, R.; et al.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Neuropharmacology (1997), 36(1), 1-11
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel compound LY354740 is a conformationally constrained analog of glutamate, which was designed for interaction at metabotropic glutamate (mGlu) receptors. In this paper the selectivity of LY354740 for recombinant human mGlu receptor subtypes expressed in non-neuronal (RGT) cells is described. At human mGlu2 receptors, LY354740 produced >90% suppression of forskolin-stimulated cAMP formation with an EC50 of 5.1 nM. LY354740 was 6-fold less potent in activating human mGlu3 receptors (EC50 = 24.3 nM). LY354740 inhibition of forskolin-stimulated cAMP formation in human mGlu2 receptor-expressing cells was blocked by competitive mGlu

receptor antagonists, including (+)-α-methyl-4-carboxyphenylglycine (MCPG) and LY307452 ((2S,4S)-2-amino-4-(4,4-diphenylbut-1-yl)-pentane-1,5-dioic acid). LY354740 had no agonist or antagonist activities at cells expressing human mGlu4 or mGlu7 (group III mGlu receptors) (EC50s > 100,000 nM). When tested at group I phosphoinositide-coupled human mGlu receptors (mGlula and mGlu5a), LY354740 did not activate or inhibit mGlu receptor agonist-evoked phosphoinositide hydrolysis at up to 100,000 nM. Electrophysiol. expts. also demonstrated that LY354740 also had no appreciable activity in cells expressing human recombinant AMPA (GluR4) and kainate (GluR6) receptors. Thus, LY354740 is a highly potent, efficacious and selective group II (mGlu2/3) receptor agonist, useful to explore the functions of these receptors in situ.

L9 ANSWER 141 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:188941 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 126:277738
TITLE: Synthesis, molecular modeling, and biology of the 1-benzyl derivative of APDC - an apparent mGluR6 selective ligand
AUTHOR(S): Tuckmantel, Werner; Kozikowski, Alan P.; Wang, Shaomeng; Pshenichkin, Sergey; Wroblewski, Jarda T.
CORPORATE SOURCE: Georgetown University Medical Center, Drug Discovery Laboratory, Institute for Cognitive and Computational Sciences, Washington, DC, 20007-2197, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(5), 601-606
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The synthesis of the 1-benzyl derivative of (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid (I) starting from cis-4-hydroxy-D-proline is disclosed together with a study of the activity of this compound at metabotropic glutamate receptors (mGluRs).
The title compound I (1-benzyl-APDC) was found to display good mGluR6 selectivity, and may thus be a useful pharmacol. research tool.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 142 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:124328 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 126:131199
TITLE: Design, Synthesis, and Pharmacological Characterization of (+)-2-Aminobicyclo[3.1.0]hexane-

2,6-dicarboxylic Acid (LY354740): A Potent, Selective, and Orally Active Group 2 Metabotropic Glutamate Receptor Agonist Possessing Anticonvulsant and Anxiolytic Properties

AUTHOR(S): Monn, James A.; Valli, Matthew J.; Massey, Steven M.; Wright, Rebecca A.; Salhoff, Craig R.; Johnson, Bryan G.; Howe, Trevor; Alt, Charles A.; Rhodes, Gary A.; Robey, Roger L.; Griffey, Kelly R.; Tizzano, Joseph P.; Kallman, Mary J.; Helton, David R.; Schoepp, Darryle D.

CORPORATE SOURCE: Central Nervous System Process Research and Toxicology Research Divisions, Eli Lilly and Company, Indianapolis, IN, 46285, USA

SOURCE: Journal of Medicinal Chemistry (1997), 40(4), 528-537
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (9) was designed as a conformationally constrained analog of glutamic acid. For 9, the key torsion angles (τ1 and τ2) which determine the relative positions of the α-amino acid and distal carboxyl functionalities are constrained where τ1 = 166.9° or 202° and τ 2 = 156°, resp. We hypothesized that 9 would closely approx. the proposed bioactive conformation of glutamate when acting at group 2 metabotropic glutamate receptors (mGluRs). The racemic target mol. (±)-9, its C2-diastereomer (±)-16, and its enantiomers (+)-9 (LY354740) and (-)-9 (LY366563) were prepared by an efficient, stereocontrolled, and high-yielding synthesis from 2-cyclopentenone. Our hypothesis that 9 could interact with high affinity and specificity at group 2 mGluRs has been supported by the observation that (±)-9 (EC50 = 0.086 ± 0.025 μM) and its enantiomer (+)-9 (EC50 = 0.055 ± 0.017 μM) are highly potent agonists for group 2 mGluRs in the rat cerebral cortical slice preparation (suppression of forskolin-stimulated cAMP formation) possessing no activity at other glutamate receptor sites (iGluR or group 1 mGluR) at concns. up to 100 μM. Importantly, the mGluR agonist effects of (+)-9 are evident following oral administration in mice in both the elevated plus maze model of anxiety (ED50 = 0.5 mg/kg) and in the ACPD-induced limbic seizure model (ED50 = 45.6 mg/kg). Thus, (+)-9 is the first orally active group 2 mGluR agonist described thus far and is an important tool for studying the effects of compds. of this class in humans.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 143 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:332734 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 125:19025

TITLE: Pharmaceutical compositions containing agonists which act at negatively coupled cAMP-linked metabotropic glutamate receptors for protection against drug dependency

INVENTOR(S): Helton, David Reed; Kallman, Mary Jeanne; Monn, James Allen; Schoepp, Darryle Darwin; Tizzano, Joseph Patrick

PATENT ASSIGNEE(S): Eli Lilly and Co., USA

SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604900	A1	19960222	WO 1995-US10317	19950814
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5661184	A	19970826	US 1995-496642	19950629
IN 1995CA00927	A	20050701	IN 1995-CA927	19950808
RU 2152925	C1	20000720	RU 1995-113894	19950811
AU 9533250	A	19960307	AU 1995-33250	19950814
CN 1123272	A	19960529	CN 1995-115896	19950814
CN 1066135	B	20010523		
ZA 9506773	A	19970214	ZA 1995-6773	19950814
EP 776200	A1	19970604	EP 1995-929519	19950814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, MC, NL, PT, SE				
JP 10504038	T	19980414	JP 1996-507563	19950814
JP 3618104	B2	20050209		

PRIORITY APPLN. INFO.:

US 1994-289957	A	19940812
US 1994-337349	A	19941110
US 1995-496642	A	19950629
WO 1995-US10317	W	19950814

AB Pharmaceutical compns. containing agonists which act at neg. coupled cAMP-linked metabotropic glutamate receptors are useful for the treatment of substance dependence disorders. A solution of 184 g of (-)-2-spiro-5'-hydantoinbicyclo[3.1.0]-hexan-6-carboxylic acid and 1750 mL of 3N NaOH were heated at reflux until the reaction was complete, the solution was then cooled to room temperature, filtered, the pH was adjusted to 3.0, and stirred for 1 h at room temperature and 2 h at 0° to obtain (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (I). The EC50 of I for the inhibition of forskolin-stimulated cAMP formation in rats' hippocampus and cerebral cortex was 0.035, and 0.55 μM, resp. A hard gelatin capsule contained I 250, starch 200, and Mg stearate 10 mg.

L9 ANSWER 144 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:332733 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 125:19024
TITLE: Pharmaceutical compositions containing agonists which act at negatively coupled cAMP-linked metabotropic glutamate receptors for treating anxiety
INVENTOR(S): Helton, David Reed; Kallman, Mary Jeanne; Monn, James Allen; Schoepp, Darryle Darwin; Tizzano, Joseph Patrick
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604901	A1	19960222	WO 1995-US10318	19950814
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
IN 1995CA00927	A	20050701	IN 1995-CA927	19950808
RU 2152925	C1	20000720	RU 1995-113894	19950811
CA 2195782	A1	19960222	CA 1995-2195782	19950814
AU 9533649	A	19960307	AU 1995-33649	19950814
CN 1123272	A	19960529	CN 1995-115896	19950814
CN 1066135	B	20010523		
ZA 9506773	A	19970214	ZA 1995-6773	19950814
EP 776201	A1	19970604	EP 1995-930169	19950814
EP 776201	B1	20011017		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 11507008	T	19990622	JP 1996-507564	19950814
JP 3614435	B2	20050126		
AT 206915	T	20011115	AT 1995-930169	19950814
ES 2162936	T3	20020116	ES 1995-930169	19950814
PT 776201	T	20020328	PT 1995-930169	19950814
HK 1013958	A1	20020705	HK 1998-115179	19981223

PRIORITY APPLN. INFO.:	US 1994-289957	A	19940812
	US 1994-337349	A	19941110
	US 1995-496710	A	19950629
	WO 1995-US10318	W	19950814

AB Pharmaceutical compns. containing agonists which act at neg. coupled cAMP-linked metabotropic glutamate receptors are useful for the treatment of anxiety. A solution of 184 g of (-)-2-spiro-5'-hydantoinbicyclo[3.1.0]-hexan-6-carboxylic acid and 1750 mL of 3N NaOH were heated at reflux until the reaction was complete, the solution was then cooled to room temperature, filtered, the pH was adjusted to 3.0, and stirred for 1 h at room temperature and 2 h at 0° to obtain (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (I). The EC50 of I for the inhibition of forskolin-stimulated cAMP formation in rats' hippocampus and cerebral cortex was 0.035, and 0.55 μM, resp. A hard gelatin capsule contained I 250, starch 200, and Mg stearate 10 mg.

L9 ANSWER 145 OF 145 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:264955 HCAPLUS <<LOGINID::20070726>>
DOCUMENT NUMBER: 124:317874
TITLE: Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicaroboxylates and related compounds as agonists of negatively-coupled cAMP-linked metabotropic glutamate receptors.
INVENTOR(S): Helton, David R.; Monn, James Allen; Schoepp, Darryle D.; Tizzano, Joseph P.
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW

10/562010 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID

DOCUMENT TYPE: Patent
LANGUAGE: English
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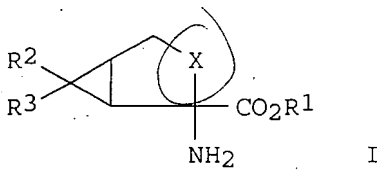
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 696577	A1	19960214	EP 1995-305632	19950811
EP 696577	B1	19981014		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5750566	A	19980512	US 1995-496643	19950629
IN 1995CA00927	A	20050701	IN 1995-CA927	19950808
RU 2152925	C1	20000720	RU 1995-113894	19950811
CN 1123272	A	19960529	CN 1995-115896	19950814
CN 1066135	B	20010523		
ZA 9506773	A	19970214	ZA 1995-6773	19950814
PRIORITY APPLN. INFO.:			US 1994-289957 A	19940812
			US 1994-337349 A	19941110
			US 1995-496643 A	19950629

OTHER SOURCE(S): MARPAT 124:317874
GI



I

AB Title compds. [I; X = (CH2)n; R2 = CO2R4 and R3 = H, or R2 = H and R3 = CO2R4; R1, R4 = H, alkyl, alkenyl, aryl, aralkyl; n = 1], were prepared Thus, (-)-2-spiro-5'-hydantoinbicyclo[3.1.0]hexane-6-carboxylic acid (preparation given) was refluxed in 3n NaOH to give 86% (+)-2-aminobicyclo[3.1.0]hexane-6-carboxylic acid. The latter inhibited forskolin-stimulated cAMP formation in rat cerebral cortex with EC50 = 0.055 μM. Dosage forms containing 2-aminobicyclo[3.1.0]hexane-6-carboxylic acid are given.

=> d his

(FILE 'HOME' ENTERED AT 14:28:26 ON 26 JUL 2007)

FILE 'REGISTRY' ENTERED AT 14:28:51 ON 26 JUL 2007
L1 STRUCTURE UPLOADED
L2 39 S L1
L3 730 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 14:29:28 ON 26 JUL 2007
L4 190 S L3
L5 21 S L2
L6 4615 S "METABOTROPIC GLUTAMATE RECEPTOR"
L7 145 S L6 AND L3
L8 19 S L6 AND L5
L9 145 S L6 AND L4